

Epstein-Barr virus-related lymphoproliferative disorders of the skin

Gerardo Ferrara, Alberto Gualandi

Anatomic Pathology and Cytopathology Unit, G. Pascale Foundation National Cancer Institute IRCCS, Naples, Italy

Abstract

Epstein Barr Virus (EBV) is associated both solid (nasopharyngeal carcinoma, non-nasopharyngeal lymphoepithelioma-like carcinoma, gastric carcinoma, leiomyosarcoma) and hematolymphoid malignancies, some of the latter, however, spanning over a spectrum ranging from reactive and self-limiting to severe and life-threatening conditions. This review will focus on the disorder most commonly involving the skin, namely: EBV-positive mucocutaneous ulcer; lymphomatoid granulomatosis; EBV-positive diffuse large B cell lymphoma; plasmablastic lymphoma; post-transplant lymphoproliferative disorder; extranodal NK/T cell lymphoma, nasal type; angioimmunoblastic T cell lymphoma; severe mosquito bite allergy; hydroa vacciniforme-like lymphoproliferative disorder. Given the uncommon occurrence of all these infiltrates in the skin, multidisciplinary approach, as well as referral to tertiary care centers are always advisable.

Introduction

Epstein Barr virus (EBV), or Human Herpesvirus 4, is a ubiquitous herpesvirus which is associated to a variety of human malignancies, both solid (nasopharyngeal carcinoma, non-

nasopharyngeal lymphoepithelioma-like carcinoma, gastric carcinoma, leiomyosarcoma) and hematolymphoid (Table 1).¹ Infectious mononucleosis is the acute infection; it is transmitted from the carrier through saliva and infects naïve tonsillar B cells via interaction of the viral glycoprotein gp350 and CD21/CD3d on B cells; lytic infection can produce new viral particles and epithelial cells can also become infected. The virus then enters a latent phase in the periphery via late membrane proteins (LMPs) 1 and 2a, Epstein-Barr nuclear antigens (EBNAs) and Epstein-Barr encoded RNAs (EBERs) (latency III); this status is highly immunogenic and allows the immune system to overcome the acute infection.² Like other herpesviruses, however, EBV establishes an asymptomatic, life-long latent infection, with occasional reactivation: infected B-cells progress through germinal center reactions in latency II where LMP1 and LMP2a can provide surrogate signals for CD40 (tumor necrosis factor) and B-cell receptor signaling, respectively. EBV+ B-cells emerge from the germinal center and EBV persists in a subset of memory B cells without viral gene expression (latency 0) or with EBNA1 expression (latency I) during cell division. Latency 0-I is the least immunogenic status. Periodic reactivation of the virus can occur leading to production of new viral particles.³ Infection of T-cells can take place as well as the following expression of CD21/CD3d by T-cells during thymic differentiation; or following ‘trogocytosis’ (exchange of plasma membrane patches carrying Ag-Ab complexes); or following internalization of the virus following a killing attempt. EBV+ T/NK LPDs are generally characterized by a latency II transcriptional program with EBNA-1, LMP-1 and LMP-2b, EBERs, BARTmiRNA, and BHRF1miRNA.⁴

EBV 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 cell. These effects are mediated by EBNSAs and LMPs which function as transcriptional coactivators, signaling molecules, and epigenetic modifiers (EBNAs, LMP-1) Furthermore, the immediate early gene BZLF1, which activates EBV’s lytic cycle, directly promotes lymphomagenesis.⁵ The classification of the various EBV-induced/associated lymphoproliferative disorders is based on the lineage of the target cells, *i.e.*, B, T, and NK-cells (Table 1); even if all of them can potentially involve the skin as a consequence of a systemic disease,⁶ some of them (highlighted in bold in Table 1) can primarily arise in the skin.⁷ Starting from technical issues related to the search for EBV on tissue samples, this review will focus of the EBV-related lymphoid proliferations which can primarily or secondarily involve the skin.

Technical issues

The classical clinicopathological settings that should prompt Pathologists to look for EBV antigens or nucleic acids in lymphoid cell infiltrates of the skin are the following: i) immune deficiency; ii) young patients with photosensitivity; iii) old patients; iv) patients with concomitant nodal or pulmonary involvement; v)

Correspondence: Gerardo Ferrara, Anatomic Pathology and Cytopathology Unit, Istituto Nazionale Tumori I.R.C.C.S. Fondazione ‘G. Pascale’, via Mariano Semmola, 53, I80131 Naples, Italy.

E-mail: gerardo.ferrara@libero.it

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lymphoid infiltrates with prominent angiocentrism/angioid invasion/angiodestruction and with extensive, infarct-like necrosis; vi) lymphoid infiltrates with prominent CD56 and/or cytotoxic marker expression.⁸ The most abundant viral transcripts in latently infected cells, EBER-1 and EBER-2, are non-polyadenylated and thus, are not translated into protein; they function to inhibit interferon-mediated antiviral effects and apoptosis. These two transcripts, collectively called EBERs, are expressed at such high levels (around a million copies per latently infected cell) that they are considered to be the best natural marker of latent infection. *In situ* hybridization targeting one or both EBERs is the gold standard assay for determining whether a biopsied tumor is EBV-related. The single most informative protein-based assay is immunohistochemistry because it is feasible in paraffin-embedded sections for latent and lytic viral factors including EBNA1, EBNA2, LMP1, LMP2, BHRF1, BZLF1, and BMRF: their evaluation complements EBER *in situ* hybridization for diagnosis of EBV-related disease by helping detect the latency pattern (Table 2).^{8,9} From latency 0-I to latency III, along with the increasing immunogenicity, there is an increasing immune suppression associated with the respective neoplastic diseases.

Epstein Barr virus-positive mucocutaneous ulcer

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. The cutaneous involvement is often peri-oral/buccal but other acral sites or the trunk may be affected. Typically, there is no systemic lymphadenopathy and/or splenomegaly; EBV-DNA is typically undetectable in peripheral blood, even in post-transplant cases, in contrast to many other

types of EBV-associated lymphoproliferative disorders.^{10,11}

Histopathologically, there is a shallow sharply circumscribed ulcer with epidermal pseudoepitheliomatous hyperplasia and a polymorphous infiltrate, with small lymphocytes concentrated at the ulcer base, immunoblasts, plasma cells, eosinophils, and histiocytes. Diagnostic features are: i) Reed-Sternberg-like cells; ii) 'Plasmacytoid' apoptotic cells (cells with abundant basophilic cytoplasm and radial distribution of clumped chromatin in apoptotic nuclei. Angioinvasion and surrounding necrosis are common. The immunophenotype of Reed-Sternberg-like cells is CD20+; CD15+/-; CD30+; CD79a+; MUM1+; EBV+.

Clonality studies can show rearrangements of the B- and T-cell receptor in 39% and 38% of cases, respectively.¹²⁻¹⁴

The disease follows an indolent course, sometimes with spontaneous regression; reduction in immunosuppression may be required.¹⁵

Lymphomatoid granulomatosis

This is a rare angiocentric and angiodestructive EBV+LPD with a predilection for the lungs, kidneys, central nervous system, and, in approximately half of cases, the skin.

Lymphomatoid granulomatosis (LyG) typically presents in the 4th to 6th decade of life and has a slight male predominance; it can occur in association with constitutional immune-deficiency syndromes such as Wiskott-Aldrich, myeloproliferative neoplasms, and in post-transplant settings. In the setting of immune deficiency, the differential diagnosis with other EBV+ B-LPD is challenging. B-symptoms are present in 80% of patients. The cutaneous lesions can precede, coincide or follow the pulmonary lesions; the elementary lesions are papules, plaques, nodules, ulcers, or, else, inflamed hair follicles (folliculitis).^{16,17}

Histopathologically, cutaneous lesions of LyG show a nodular, angiocentric/angiodestructive lymphoid or lymphohistiocytic

Table 1. Classification of Epstein Barr virus-related lymphoproliferative disorders.

B-cell lineage	T/NK-cell lineage
<ul style="list-style-type: none"> <i>EBV-positive mucocutaneous ulcer</i> <i>Lymphomatoid granulomatosis</i> <i>EBV-positive diffuse large B-cell lymphoma</i> <i>Plasmablastic lymphoma</i> <i>Post-transplant lymphoproliferative disorders</i> Primary effusion lymphoma (and its solid variant) Burkitt lymphoma (endemic variant) Hodgkin lymphoma X-linked lymphoproliferative disease with hemophagocytic lymphohistiocytosis 	<ul style="list-style-type: none"> <i>Extranodal NK/T-cell lymphoma, nasal type</i> <i>Angioimmunoblastic T-cell lymphoma</i> <i>Severe mosquito bite allergy</i> <i>Hydroa vacciniforme-like lymphoproliferative disorder</i> Systemic chronic active EBV infection of T-cell or NK-cell type <i>Aggressive NK-cell leukemia</i> <i>Peripheral T-cell lymphoma, not otherwise specified</i>

Entities with a possible cutaneous involvement are highlighted in *italics*. PTCL-NOS is not included in this review because being a diagnosis by exclusion. EBV, Epstein Barr virus; T/NK, T-cell/natural killer.

Table 2. Interpretation of the latency type of Epstein Barr virus infection and associated status/disease.

Latency	EBERs	EBNA1	EBNA2	EBNA3	LMP1	LMP2	Status/disease
0	+	-	-	-	-	-	Carrier
I	+	+	-	-	-	-	Burkitt lymphoma
II	+	+	+	+	+	+	Nasopharyngeal carcinoma, Hodgkin lymphoma
III	+	+	-	-	+	+	Infectious mononucleosis, lymphoproliferative disease
Other	+	+/-	-	-	-	+/-	Carrier

EBER, Epstein-Barr encoded RNA; EBNA, Epstein-Barr nuclear antigen; LMP, late membrane protein.

infiltrate with or without multinucleated giant cells. The number of EBV-positive cells, as well as the amount of necrosis are the criteria for Lipford's grading of LyG:

Grade 1: <EBV-positive large B-cells/ Histologically, cutaneous lesions of LyG shows a nodular, angiocentric/angiodestructive lymphoid or lymphohistiocytic infiltrate with or without multinucleated giant cells. A lymphohistiocytic panniculitis is characteristic, with poorly formed granulomas; neoplastic EBV-positive large cells may be few or even absent. The number of EBV-positive cells, as well as the amount of necrosis are the criteria for Lipford's grading of LyG; no necrosis;

Grade 2: 5-50 EBV-positive large B-cells/high power field (HPF); focal necrosis;

Grade 3: >50 EBV-positive large B-cells/HPF; extensive necrosis.

However, the pathobiology of the cutaneous lesions appears not be directly related to EBV;¹⁸ therefore, grading of LyG in the skin is not encouraged.⁶

Lesions of polymorphic post-transplant lymphoproliferative disorders (PTLD) are relatively T-cell depleted, lack angiotropism, and are accompanied by EBV viremia.¹⁶

The differential diagnosis of LyG is broad and includes both neoplastic and non-neoplastic conditions. Granulomatosis with polyangiitis (GPA; Wegener granulomatosis) most typically involves the lung and skin. 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 EBV-positive blasts present in LyG are not seen in GPA.¹⁹

Sheet-like growth of large EBV-positive B-cells with a paucity of T-cells favors EBV + diffuse large B-cell lymphoma (DLBCL) over LyG.^{16,18}

Regarding the prognosis of LyG, spontaneous recovery occurs in about 20% of patients with low-grade (grade 1) disease, which is most likely a (dys-)reactive disorder. The reported 5-year mortality rates have been between 38% and 88%. The median survival is between 14 and 72 months.¹⁶

Epstein-Barr virus-positive diffuse large B-cell lymphoma

Originally considered to be restricted to the elderly, it is now recognized that some cases occur in younger individuals. Immune senescence is thought to play a role in most cases. EBV-DLBCL has a striking predilection for extranodal sites (70%), and particularly the skin, lung, tonsils, and stomach.

The cutaneous lesions present as plaques, tumors and nodules that are usually non-ulcerated, and with a predilection for the lower extremities.²⁰ Two main patterns are reported, polymorphous and monomorphous. 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; the monomorphous type is characterized by sheets of immunoblasts with fewer inflammatory cells. Necrosis is uncommon in cutaneous lesions.

The immunophenotype of the EBV-positive 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.²¹

The differential diagnosis is with cutaneous diffuse large cell

lymphoma, leg type, with is EBV-negative by definition; and with plasmablastic lymphoma (PLB), which is nearly always negative for the common B-cell markers (PAX-5, CD19, CD20).²²

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.²³

Plasmablastic lymphoma

PLB typically presents in the oral cavity of patients with HIV (69% of cases), and other types of immune-suppression syndromes.²⁴

Cutaneous PBL presents as non-specific lesions (erythematous nodules, infiltrated plaques). 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. The malignant cells typically lack the common B-cell antigens, while expressing the plasma cell markers CD38, CD138, CD79a, MUM1/IRF4, and BLIMP1. CD30 and EMA are frequently expressed. HHV-8 is characteristically negative, which can help in the distinction of primary effusion lymphoma and large cell lymphomas arising in the setting of Castleman disease. MYC rearrangement is seen in up to 50% of cases, thus raising the differential diagnosis with a cutaneous involvement of systemic diffuse large B cell, 'double hit' lymphoma, which is however typically EBV-negative. Rearrangement of the ALK-MPM1 gene in a few visceral cases; in such a setting, it must be remembered that true ALK+ B cell lymphomas are CD20-negative like PBL, but EBV-negative.^{25,26}

Cutaneous post-transplant lymphoproliferative disorders

PTLD can occur in 1-6% of solid organs, and less frequently hematopoietic stem cell transplant patients as a broad spectrum of clinical behaviors ranging from an infectious mononucleosis-like picture to that of an aggressive non-Hodgkin lymphoma, often with extranodal involvement.

EBV-naive patients who acquire a primary EBV infection after the transplant are at the highest risk for developing PTLT. The most common sites of involvement are: the gastrointestinal tract, lungs, central nervous system, and allografted organs.

Approximately 22% of PTLT cases show cutaneous involvement, mostly in the setting of renal transplantation. Cutaneous lesions of PTLT involve ulcers, nodules, and erythematous plaques of face, trunk, and extremities.²⁷

Polymorphic PTLT shows a mixed population of immunoblasts, plasma cells, intermediate-sized lymphoid cells (incorporating a full range of B-cell morphology and differentiation), as well as occasional Hodgkin Reed Sternberg-like cells. B-cells are usually monotypic and even if polytypic, show clonal pattern of IgH or episomal EBV genome. Morphology and immunophenotype are the same as the corresponding non-post-transplant counterpart. Regression in response to reduction in immune suppression is possible, but commoner is progression to monomorphic B-cell PTLT in the form of DLBCL, plasmacytoma, plasmablastic lymphoma, or LyG.²⁸

A variety of subtypes of T-cell lymphoma can present as monomorphic PTLID in the skin; these can be EBV-positive or negative, ranging in some series from 16% up to 60%. Monomorphic T-cell PTLIDs mirror the immunophenotypes present in sporadically occurring cases.²⁹

In early and polymorphic cases, reduction in immunosuppressive therapy can result in a cure rate of approximately 25% to 50%. Second-line therapies include: monoclonal antibodies against B-cells, cytotoxic chemotherapy, radiation therapy, donor lymphocyte transfusion, interferon therapy, antiviral medications, and intravenous immunoglobulin.^{27,30}

Extranodal NK/T-cell lymphoma, nasal type

ENKTL is an angioaggressive lymphoma with NK or cytotoxic T-cell phenotype with a strong predilection for Asians, and for Native South Americans. It is typified by extranodal (frequently upper aero-digestive) infiltration by EBV-infected lymphocytes, with vascular invasion and prominent necrosis.³¹

Clinically the disease presents in extranodal sites, mostly in the upper aerodigestive tract, including the nasal cavity (by far the most frequent site; 'lethal midline granuloma'), orbital soft tissue, paranasal sinuses, and palate. Some cases can also present in an extranasal location, although lymph node involvement is uncommon. Skin involvement is present in 10% of cases of ENKTL and manifests as ulcerated nodules, erythematous maculopapular lesions, cellulitis, and abscess-like swelling of the legs and the trunk.^{32,33}

Histologically, the angiocentric/angiodestructive pattern is found in 69% of cases of cutaneous involvement, and thus the diagnosis may be easily missed on small biopsy specimens, in which inflammatory cells can predominate. The lymphoid cell infiltrate has a broad cytomorphology, with small, intermediate or large cells, including occasionally anaplastic morphology. The nuclei can be round or folded, have coarse or vesicular chromatin, and small inconspicuous nucleoli. Areas of geographic necrosis can be present. Background inflammatory cells are variable. In the skin, linear epidermotropism can be found. Hypodermotropism can be characterized by rimming of adipocytes by atypical lymphocytes as observed in primary cutaneous gamma-delta T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma.

ENKTL has typically a cytotoxic phenotype, with expression of cytotoxic granules (granzyme B, TIA-1, and perforin). Most cases are derived from NK cells: they are thus CD56-positive and surface CD3-negative, yet positive for cytoplasmic CD3 subunits including CD3 ϵ and CD3 ζ . Most cases are positive for CD2, CD43, CD45RO, HLA-DR, CD25, CD7, and FAS (CD95) and negative for CD4, CD5, CD8, TCR γ , β F1, CD16, and CD57. EBER-positivity is a *sine qua non* for the diagnosis. 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.

The T-cell receptor (TCR) and immunoglobulin heavy chain genes are in germline configuration in ENKTL derived from NK cells, whereas cases of cytotoxic T-cell origin (10-40% of cases) show clonal rearrangements of the TCR genes.³⁴

The differential diagnosis of ENKTL in the skin includes other types of cutaneous lymphoma which may be CD56-positive and CD4-CD8 double negative (primary cutaneous $\gamma\delta$ T-cell lymphoma, blastic plasmacytoid dendritic cell neoplasm, mycosis fungoides, type E lymphomatoid papulosis) but as a rule all these disorders are EBER-negative. Aggressive NK-cell leukemia

shares similar immunophenotypic features to ENKTL, but leukemic involvement of the skin is very rare.⁶

Angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma (AITL) is follicular helper T-cell malignancy which accounts for 15-20% of peripheral T-cell lymphomas and 1-2% of non-Hodgkin lymphomas. Affected patients are mostly middle-aged to old (median age: 62-65 years) with no gender predilection. The clinical presentation is usually lymphadenopathy (mediastinal, retroperitoneal) and hepatosplenomegaly; thrombocytopenia, hemolytic anemia, and hyper-gammaglobulinemia are often detected. Constitutional symptoms are present in in >70% of patients.³⁵

Cutaneous involvement is invariably secondary; clinical features are non-specific morbilliform rash (up to 50% of cases), as well as nodules, plaques, ulcers, petechiae, and, rarely, erythroderma. Different from its nodal counterpart, cutaneous involvement by AITL is characterized by a band-like and/or perivascular infiltration of small to medium-sized T cells with minimal epidermotropism, as well as reactive histiocytes, plasma cells, and/or eosinophils. Histologic picture of vasculitis is common; epidermotropism is absent.

Characteristic findings in nodal AITL, such as atypical lymphocytes with clear cytoplasm and capillary hyperplasia are exceptional in the skin. Thus, cutaneous lesions from AITL may consist of sparse perivascular lymphocytic infiltrates without obvious atypia. Clinical information is of paramount importance in such a deceptively bland setting; newly formed vessels can be a histopathological clue prompting an immunophenotypic study. It is suggested that at least 2 out of the 3 follicular helper markers PD1, CXCL13 and ICOS must be positive within the infiltrate; CD4, CD10, and bcl6 can further aid the immunohistochemical recognition of neoplastic cells. CD30-positive large B cells, which are usually EBER-positive in nodes, are exceptional in the skin; thus, EBER is most commonly negative in skin infiltrates of AITL.

The main differential diagnosis of cutaneous AITL is with inflammatory dermatoses; in addition, primary cutaneous CD4+ small/medium T cell lymphoproliferative disorder can share with AITL some immunomorphological features, comprising the widespread positivity to follicular T helper markers, but it typically presents as a slowly-growing, solitary skin lesion with no systemic involvement.^{36,37}

Severe mosquito bite allergy

Severe mosquito bite allergy is a cutaneous manifestation of chronic active EBV infection precipitated in infants and young (<20-year-old patients) by mosquito bites or vaccination. Most cases arise in individuals from Asia and Mexico. This is not an allergic disease, but rather a cutaneous manifestation of chronic active Epstein-Barr virus infection of NK-cell lineage, with oligoclonal or monoclonal populations of NK-cells.

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. Histologically, the skin shows a vasculitis with ulceration, dermal edema and infiltration by neutrophils mononuclear cells. The latter feature a mixture of CD4 +, CD8 + T-cells and

NK-cells. EBV-positive cells represent a minority of the infiltrate (<10%).³⁸ The prognosis is variable: some patients behave in an indolent fashion while others progress to frank lymphoma.³⁹

Hydroa vacciniforme-like lymphoproliferative disease

This is a chronic EBV+ LPD of childhood with a risk of progression to systemic lymphoma. It has been proposed in recent years that T/NK-cell lymphoproliferations with HV-like cutaneous manifestations span over a spectrum with a classic, self-resolving HV at one end and HV-like lymphoma with an aggressive clinical course at the other end. In the middle of the spectrum are cases with a considerable clinical and pathological overlap between cases originally designated “classical HV” and “HV-like lymphoma”.^{40,41}

Classic HV is a rare, intermittent ultraviolet light-induced vesiculopapular and scarring eruption, that typically remits after adolescence. Systemic symptoms are not usually present in this disease. It has been proposed that certain populations (e.g., Asian and South American) can be at high risk for the development of lymphoma, whereas in others (North American and European) the disease has a very indolent course.

Clinically, classical HV is characterized by an itchy erythematous eruption in sun-exposed areas that occurs minutes to hours after sun exposure. The eruption progresses from papules to vacciniform (pox-like) vesicles and scars. Marked facial edema is a hallmark of aggressive forms. Extracutaneous involvement (hepatosplenomegaly, lymphadenopathy, bone marrow infiltration) with systemic symptoms upgrades the diagnosis to EBV+ T-cell lymphoma of childhood.⁴²

In the hydroa vacciniforme-like lymphoproliferative disease, 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. Spongiosis and intraepidermal vesicles are also seen. Progression may be heralded by cells with features recalling ENKTL, but, different from the latter, atypical CD56+ EBER+ cells are not arranged in compact sheets. Epidermotropism, subcutaneous involvement (without ‘rimming’) and angiodestruction can be present.

The EBV-infected cells can be cytotoxic T-cells (CD3+, CD8+, TIA-1+, granzyme B+, perforin+) or NK-cells (CD56+). The Ki67 labeling is variable from low to up to 50%.⁴³

Conclusions

The spectrum of EBV-induced lymphoid proliferations of the skin is very broad and, in several cases, ‘borderline’ between reactive and malignant features. The histopathological diagnosis is the guide for clinical management; nevertheless, given the overlapping features of several entities described herein, a multidisciplinary approach is always warranted. Also, given the rarity of such diseases, referral to tertiary care centers is always advisable.

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