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Infectious Agents and Cutaneous Lymphoproliferative Disorders: Myth or Reality?

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Abstract

The underlying pathogenetic mechanisms of cutaneous lymphoproliferative disorders are yet to be elucidated. Lymphogenesis is a complex process that may have several influencing factors: tumor-dependent, host-dependent, environmental, and genetic ones. Infectious agents would interact with these factors in order to boost tumor development and progression. Recently, it has been suggested that an infectious agent may initiate chronic inflammation and thus facilitating B lymphocyte transformation and lymphogenesis. Several viruses, like Epstein-Barr virus, as well as parasites and bacteria have been linked to the development of lymphomas. Some bacteria have been suggested to be carcinogens and tumor promoters by activating intracellular signaling pathways, modulating apoptosis and cell proliferation. This phenomenon occurs when the cells of the immune system are at risk of malignant transformation. Staphilococcus aureus has been identified to cause severe infections and also to play an important role in the pathogenesis of Mycosis fungoides and Sézary syndrome. The susceptibility of infection seems to be related to barrier dysfunction and immunosuppression. *Borrelia burgdorferi* has also been associated with primary cutaneous lymphomas, both B-cell and T-cell, with geographical differences. In this article, we will review the role and mechanisms of infectious agents to drive neoplastic transformation in cutaneous lymphoproliferative disorders.

Keywords: Lymphoproliferative disorders; Infectious agents; Cutaneous lymphomas

Abbreviations: NHL: Non-Hodgkin B-Cell Lymphomas; MZL: Marginal-Zone Lymphomas; DLBCL: Diffuse Large B-Cell Lymphoma; CBCLs; Cutaneous B-cell Lymphomas; MF: Mycosis fungoides; EBV: Epstein-Barr virus; TEWL: Transepidermal Water Loss; AMP: Antimicrobial Peptide; SEs: Staphylococcal Enterotoxins; TSST-1: Toxic Shock Syndrome Toxin; TR: T cell Receptor; SAF: Sézary T cell Activating Factor; HTLV: Human T-Lymphotropic Virus; LPD: Lymphoproliferative Disorders; EBER: EBV-encoded mRNA; PC-ENKTL: Primary Cutaneous Extranodal Natural Killer/T-Cell Lymphoma; HV: Hydroa Vacciniforme; HHV: Human Herpesvirus 8; KSHV: Kaposi Sarcoma-Associated Herpesvirus; CMV: Cytomegalovirus; MCV: Merkel Cell Polyomavirus; MCC: Merkel Cell Carcinoma; MRSA: Methicillin Resistant *S. aureus*; DLBCL: Diffuse Large B-Cell Lymphoma; MZL: Marginal Zone Lymphoma; FL: Follicular Lymphoma; AITL: Angioimmunoblastic T-Cell Lymphoma; HCV: Hepatitis C Virus.

Introduction

Primary cutaneous lymphomas (PCLs) are a heterogeneous group of non-Hodgkin lymphomas arising initially in the skin, with no evidence of extracutaneous disease at the time of the diagnosis, with some exceptions [1]. It has been reported that 27% of non-Hodgkin lymphomas occur in extranodal sites, with the skin being the second most common site of extranodal involvement after the

gastrointestinal tract [2].

According to epidemiological studies, non-Hodgkin B-cell lymphomas (NHL) are the most common hematological malignancies worldwide and the fifth most common cancer. NHL are a heterogeneous group of lymphoid neoplasms, including both latent types, such as marginal-zone lymphomas (MZL), follicular lymphomas, and also aggressive diseases such as diffuse large B-cell lymphoma (DLBCL) and Burkitt's lymphoma [3].

PCLs can arise from T or B lymphocytes, termed cutaneous T-cell lymphomas (CTCLs) or cutaneous B-cell lymphomas (CBCLs), respectively. 75-85% of PCLs are T-cell derived, opposite to nodal non-Hodgkin lymphomas or extranodal non-Hodgkin lymphomas, most of which are B-cell derived [4]. Large epidemiological studies have identified the incidence of PCLs to be 0-7-2 per 100.000 population [5,6].

CTCLs are malignancies of skin-trafficking T cells. Mycosis fungoides (MF), clinically characterized by patches, plaques, and tumors, and Sézary Syndrome (SS), characterized by leukemic involvement, represent the commonest types of CTCLs [7]. In patients with advanced CTCL, immune dysfunction predisposes to infection and suppresses the anti-tumor immune response [8].

As we know, several cancers are originated by infectious agents. Some of them may trigger carcinogenesis indirectly, activating chronic infection and inflammation. Helicobacter pylori (H. pylori) can act as an indirect carcinogen leading to gastric cancer, and hepatitis B and C viruses may be indirect carcinogens in hepatocellular carcinoma. Human papillomaviruses and Epstein-Barr virus (EBV) may trigger oncogenesis by direct mechanisms, deploying mutagenic effects and leading to malignant transformation [9]. The underlying pathogenetic mechanisms of cutaneous lymphoproliferative disorders are yet to be elucidated.

Several factors have been described related to lymphogenesis: tumor-dependent, host-dependent, environmental, and genetic ones. Infectious agents would interact with all these factors to promote tumor development and progression [10]. Recently, it has been suggested that an infectious agent may initiate chronic inflammation and facilitate B lymphocyte transformation and lymphogenesis [3].

Several viruses, like Epstein-Barr virus, as well as parasites and bacteria have been linked to the development of lymphomas. Some bacteria have been suggested to be carcinogens and tumor promoters by activating intracellular signaling pathways, modulating apoptosis and cell proliferation [11]. This phenomenon occurs when the cells of the immune system are at risk of malignant transformation [12].

Staphylococcus aureus has been identified not only to cause severe infections but also to play an important role in the pathogenesis of *Mycosis fungoides* and Sézary syndrome. The susceptibility of infection is related to barrier dysfunction and immunosuppression [1]. *Borrelia burgdorferi* has been associated with primary cutaneous lymphomas, both B-cell and T-cell, with strong geographical differences [13]. However, a recent paper did not find a relationship between *B. burgdorferi* and the occurrence of cutaneous B-cell lymphomas in endemic areas, despite a highly sensitive Borrelia PCR assay [14].

In this article, we will review the role and mechanisms of infectious agents that have been shown to drive neoplastic transformation in cutaneous lymphoproliferative disorders. Controversial and diverging hypotheses will also be reviewed in order to have a comprehensive update on the topic.

Barrier Dysfunction and Immune Dysfunction in CTCL

In CTCL, the risk of infection is high, contributing in some cases more to mortality than the malignancy per se [8]. A large retrospective cohort study found that staphylococcal, streptococcal and herpetic skin infections are, in decreasing order, the most common in MF and SS [15]. Rarer infectious complications, such as progressive multifocal leukoencephalopathy (PML), *P. jirovecii* pneumonia and toxoplasmosis have also been observed but to a lesser extent than bacterial and herpesvirus infections [15,16].

The disruption of epidermal barrier promotes skin colony formation by microorganisms. *S. aureus*-positive patients show higher transepidermal water loss (TEWL) than *S. aureus*-negative ones [17]. TEWL increases with bacterial load, and the lesional skin of patients with CTCL has higher TEWL than normal skin [18]. CTCL lesional skin contains lower levels of filaggrin and loricrin mRNA than normal skin. Moreover, mRNA expression levels of filaggrin in CTCL negatively correlate with disease severity markers [17].

In patients with CTCL, cutaneous bacterial infections appear due to impaired antimicrobial peptide (AMP) induction [17,19]. The risk of infection in CTCL also requires a maximal decrease in normal circulating T cells [20]. The absence of a Th1 immune response together with the increase of a Th2 immune response trigger the growth of

S. aureus on CTCL skin [21]. Patient's T-cell repertoire is almost entirely limited to the tumor cell repertoire and, as the stage of CTCL progresses, local infections can spread and become lethal [22]. In patients with MF/SS a clonal growth of the malignant T cell population and a severe disruption of their whole T cell repertoire can be observed. Most cases with advanced disease and in half of those with early-stage disease show an extreme disruption of the complexity of T-cell repertoire. As a consequence of the suppression of host antitumor immunity, together with the reduction of immune surveillance against pathogens, the number and activity of NK cells and the number of CD8-positive T cells decrease with the progression of CTCL [23].

Disease progression may also be stimulated by microbial. For instance, in patients with erythrodermic CTCL there is a high incidence of colonization with *S. aureus* strains producing superantigenic staphylococcal enterotoxins (SEs) or toxic shock syndrome toxin (TSST-1) [24]. The activation of STAT3 and the expression of IL-17 in CTCL cell lines can be related to bacterial isolates from patients and recombinant SEs [25]. The expression of the regulatory T cell (Treg) marker FOXP3 in SS cells, in a STAT5 dependent manner, may also be triggered by SEs [26]. Moreover, the oncogenic microRNA miR-155 is STAT5 dependent, too, which raises the possibility that SEs could contribute to the high expression of this molecule in CTCL cells [27]. A subset of T cell receptor (TR) variable region β chains are responsible to specific SEs or TSST-1 [28]. However, in patients colonized with toxicogenic *S. aureus* strains these TCRs are overrepresented in the expanded clones of CTCL [24]. Toxins may activate benign cells which then stimulate neighboring malignant cells even when the clonal TCR is unresponsive to SE [25,29]. Furthermore, benign T cells are sensitive to cell death induced by *S. aureus* alpha toxin, whereas malignant cells are resistant [30]. Finally, in SS patients polymorphonuclear granulocytes (PMNs) have shown to have reduced phagocytic activity and intracellular killing against K. pneumonia [31]. Defects in antigen presenting cells (APCs) and in innate immunity also contribute to the development of infections in these patients.

In the occurrence of certain comorbidities, CTCL seems to be more common and may be more aggressive. For instance, a 15-fold higher incidence of T cell lymphomas in AIDS patients has been reported [9]. CTCL could have a particularly aggressive course in post-transplantation patients, [32]. In undiagnosed CTCL, drugs inhibiting T cell function, like anti-TNF agents and cyclosporine, can drive progression [33,34]. Finally, dupilumab, an anti-IL4 receptor antibody, may also accelerate CTCL advance through unknown mechanisms, diminishing tumor reactive lymphocytes [35]. All these associations strengthen the role of T cell immune function in controlling disease continuation.

Infectious Agents in CTCL

The role of infectious agents in the proliferation of neoplastic T cells and the development of CTCL has been supported for more than three decades [36]. MacKie published this hypothesis in 1981 by proposing that CTCL arises from an initial viral infection of epidermal antigen presenting cells [37]. This theory was reinforced by the earlier discovery of HTLV-1 and its association with adult T cell lymphoma [38].

Furthermore, some bacterial agents have been described to have a direct role in the pathogenesis of CTCL. Chlamydia chronic infection was believed to drive chronic expansion of Chlamydia-specific T cells. Moreover, the development of CTCL was related to the combination of a Sézary T cell activating factor (SAF) and chronic T cell activation [39]. However, a significant presence of Chlamydia pneumonia in CTCL skin specimens was not detected in subsequent studies [40].

Gene expression analysis of sequence-based transcriptome data has shown upregulation of 216 agents involved in infectious disease pathways associated with viral, bacterial, and parasitic infections [41]. The pathway which is most closely associated with the CTCL transcriptome is the reaction to viral infection. The activation of this pathway produces an antiviral and antistress response to a variety of pathogens, including viral dsRNA and bacterial lipopolysaccharides [42]. Otherwise, these pathways could be important to CTCL pathogenesis secondarily, contributing to immune response dysregulation that occurs after pathogenesis.

Infectious agent	CTCL	Association found
HTLV	MF/SS	No [41,47,48]
EBV	MF/SS	No [52-55]
EBV	PC-ENKTL	Yes [56]
KSHV/HHV-8	MF	No [55]
HHV-6, HHV-7	MF/SS	No [52,53,60,61]
CMV	MF/SS	No [62,63]
MCV	MF/SS	No [9]
HPyV6, HPyV7, HPyV9, HPyV12, and MWPyV	MF/SS	No [64]
Cutavirus	MF/SS	Yes [65,66]
S. aureus	MF/SS	Yes [67-72]
B. burgdorferi	MF	Yes [75]

Table 1: Shows the infectious agents that have been studied in CTCL.

Viral Infection

Retroviruses

Retrovirus-like particles in Langerhans cells occupying the skin and lymph nodes of patients with MF and SS were described by Van der Loo, et al. [43], contributing to MacKie's hypothesis [37]. This observation was further driven by the discovery of human T-lymphotropic virus (HTLV), causing adult T-cell leukemia and lymphoma. HTLV became a subject of study as a possible trigger factor of CTCL, since CTCL has significant clinical and histopathological similarities to its nodal correspondent [9].

Retrovirus-like particles and reverse transcriptase activity ion a cell line derived from a patient with SS were observed by Manzari, et al. [44]. They isolated HTLV-V, a novel retrovirus related to HTLV-I and HTLV-II., and Zucker-Franklin, et al. [45,46] found HTLV-like inclusions in the peripheral blood mononuclear cells of patients with CTCL. Moreover, these authors also described HTLV proviral sequences and reverse transcriptase activity in some cell lines derived from peripheral blood mononuclear cells of patients with MF and SS, suggesting a potential role of HTLV-II and HTLV-I in CTCL.

Nevertheless, subsequent studies failed to amplify HTLV genomic sequences or to detect anti-HTLV antibodies in patient [47,48]. More recently, O'Neill Dulmage, et al. [41] concluded that HTLV-I is not a directly oncogenic virus in CTCL pathogenesis. However, they did not exclude the possibility that concurrent infection with HTLV-I could contribute to a chronic antigen stimulation model which has long been proffered [49].

Finally, recent investigations have suggested a connection between human endogenous retrovirus-reactive antibody titer and CTCL disease severity. Pericentromeric instability, defining the high frequency of deletions in the pericentromeric area of our genome, is associated with more severe CTCL in Caucasian, allowing T-cells to survive lysis by HIV infection [50]. In lymphomatoid papulosis, a subset of CTCL, reverse transcriptase and human endogenous retrovirus transcripts have been detected [51]. However, a causal relationship needs to be established.

Herpesviruses

Controversial results on genomic sequences of EBV detected in CTCL lesional and blood samples have been published [52-55]. The presence of EBV association, demonstrated by in situ hybridization for EBV-encoded mRNA (EBER), can be found in primary cutaneous extranodal natural killer/T-cell lymphoma (PC-ENKTL) [56]. Chronic active EBV infection (CAEBV) and systemic EBV+ T-cell lymphoma of childhood are included in EBV-associated T- and NK-cell lymphoproliferative disorders (LPD). Hydroa vacciniforme (HV)-like LPD is a primary cutaneous form of CAEBV [57].

Trento, et al. [58] found a high prevalence of Kaposi sarcoma-associated herpesvirus (KSHV)/human herpesvirus 8 (HHV-8) infection in patients with large-plaque parapsoriasis. This finding led to analyses of CTCL tissues for evidence of KSHV/HHV-8 infection, despite previous negative reports [53,59]. Kreuter, et al [55] found that 7 of 10 analyzed MF samples were positive for HSHV/HHV-8 DNA by PCR, but this observation could not be further confirmed.

Current data fail to support a role for HHV-6 and HHV-7 in CTCL pathogenesis [52,53,60,61].

In T-cell deficient populations, such as HIV-positive patients and transplantation recipients on immunosuppressive regimen, cytomegalovirus (CMV) infection is common. Nevertheless, conflicting results have been reported in cohorts of patients with CTCL [62,63].

Polyomaviruses

Mirvish, et al. [9] found that immunohistochemical stains were negative for the Merkel cell polyomavirus (MCV) T antigen in all examined MF specimens, whereas the Merkel cell carcinoma (MCC) specimen (positive control) showed strongly positive MCV finding, suggesting that MCV is not associated with CTCL pathogenesis.

Human polyomaviruses 6 (HPyV6), human polyomaviruses 7 (HPyV7), human polyomaviruses 9 (HPyV9), human polyomaviruses 12 (HPyV12), and Malawi polyomavirus (MWPyV) were analyzed in 55 CTCL by Bergallo, et al. [64] in order to confirm the skin tropism and possible pathological association. Low-level presence of HPyV6 and HPyV7 DNA, together with lack of detection of polyomaviruses HPyV9, MWPyV and HPyV12 did not support a significant role of these viruses in the ethiopathogenesis of CTCL.

Parvoviruses

Cutavirus has been detected in human fecal samples and in 4 lesional biopsy specimens only in male patients with early-stage (IA or IB) MF [65]. Cutavirus DNA was also found in 3.2% of lymphoma biopsies and in 4.6% of patients [66].

Bacterial Infection

Staphylococcus aureus

S. aureus prevalence is increased in CTCL patients and contributes to CTCL disease flares. Skin that is colonized by *S. aureus* is associated with CTCL disease progression to erythroderma, clinical exacerbation of pruritus, and increased

lactate dehydrogenase (LDH) and malignant CD4+ T cell counts. Emge, et al. [67] conducted a retrospective review of erythrodermic CTCL patients with *S. aureus* infection or colonization. They found that methicillin-resistant *S. aureus* (MRSA) prevalence was high in erythrodermic CTCL patients and that treatment improved CTCL skin score in most cases.

Staphylococcal enterotoxins and *S. aureus* isolates from lesional skin induce the expression of the oncogenic microRNA miR-155 in primary malignant cells, as observed by Willerslev-Olsen, et al. [68]. This induction is possible partly through the IL-2Rg-Jak-signal transducer and activator of transcription 5 pathway, and the effect is augmented by the presence of nonmalignant T cells. Mycosis fungoides lesions contain *S. aureus*, express Y-phosphorilated signal transducer and activator of transcription 5 and display augmented miR-155 expression compared with nonlesional healthy skin. In patients with Sézary syndrome, aggressive antibiotic therapy is associated with decreased Y-phosphorylated signal transducer and activation of transcription 5 and miR-155 expression in lesional skin.

In patients with advanced CTCL, treatment for 10 days with intravenous antibiotics (cephalosporin and metronidazole) followed by oral treatment of 14 days with combined amoxicillin and clavulanate inhibited clinical disease activity, as published by Lindhal, et al. [69], decreasing the fraction of malignant T cells in skin lesions colonized by enterotoxin-producing *S. aureus*. Furthermore, the skin microbiome consists of complex communities of different bacterial species in addition to *S. aureus* in patients with CTCL [70,71]. Based on these findings, Lindhal, et al. [72] reexamined the bacterial flora on lesional skin of the patients with advanced disease before, during, and after aggressive antibiotic therapy as described above. Treatment was associated with a complete eradication or suppression of *S. aureus* but not of other species, but re-colonization of skin lesions by *S. aureus* was observed in the majority of patients shortly after antibiotic therapy. Therefore, there is a need for novel non-antibiotic and highly selective anti-*S. aureus* therapies to gain life-long control of *S. aureus* colonization avoiding antibiotic resistance.

Borrelia burgdorferi

Borrelia burgdorferi, mainly known as the causative agent of Lyme disease, is a spirochete that can be transmitted to man by Ixodes ticks [73,74]. Acrodermatitis chronica atrophicans, which has been associated with CBCL, is a chronic cutaneous manifestation of Lyme disease.

The prevalence of *Borrelia burgdorferi* DNA in specimens of PCL was evaluated by Travaglino, et al. [13]. Borrelia DNA positivity was significantly associated with PCL among different entities: marginal zone 7.3%, follicular 8.1%, diffuse large B-cell 7.5%, mycosis fungoides 8%. The presence of Borrelia in PCL had been previously detected in studies from endemic areas, such as Austria, Scotland and north-eastern Italy [75-77]. In the literature, 6 out of 11 cases of PCL treated with antibiotics responded, while five did not. Consequently, molecular testing and antibiotic therapy for Borrelia could be justified in patients from endemic areas.

Infectious Agents in CBCL

B-cell lymphomas account for 30% of PCL, including marginal zone lymphoma (MZL), follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL) leg-type. Chronic stimulation of B-cells by viral or bacterial antigens facilitates mutations that promote lymphomagenesis. The clinical implication is that low-grade lymphomas, particularly MZL, might be treated by eradicating the causative infectious agent [78].

Diffuse large B-cell lymphoma is the most common type of lymphoma, accounting for one-third of cases worldwide [79], the majority of them classified as not otherwise specified (NOS). About 20% of cases are designated as specific variants of DLBCL, including primary cutaneous diffuse large B-cell lymphoma, leg type, and lymphomatoid granulomatosis.

Environmental factors such as infectious agents might play a role in lymphomagenesis of B-cell non-Hodgkin lymphomas [80,81]. Lymphoid proliferation increases the risk of transformation and sustained activation of the lymphoid system, due to the instability of lymphocytes, which can be observed during chronic infection, immunodeficiency, and autoimmunity, representing a risk factor for lymphomas [82,83]. The risk of developing B-cell NHLs is higher in congenital and acquired immunodeficiencies associated with HIV infection and solid organ or hematopoietic transplantation [84,85]. Lymphomagenesis promoting favorable conditions for lymphocyte transformation, like increased proliferation or decreased apoptosis of lymphoid cells, have been associated to infectious agents [86].

Lymphomas driven by infectious agents may occur from direct lymphocyte transformation by a microbial agent. Lymphotropic transforming viruses such as EBV, HHV8, and HTLV-1 directly infect a subgroup of lymphoid cells expressing viral oncogenes [87-89]. Microbial species associated with lymphomas that do not directly infect or transform lymphoid cells but have the capacity to persist chronically in host tissues and activate a sustained lymphoid proliferation, giving a selective advantage to lymphoid clones that remain dependent upon antigen stimulation

[90,91]. Thus, the microbial agent acts as a chronic source of antigens rising the proliferative rate of lymphoid effectors and sustaining the transformation process [92].

Infectious agent	CBCL	Association found
EBV	EBV-positive DLBCL	Yes [94-96]
HIV	DLBCL	Yes [93]
KSHV/HHV8	DLBCL	Yes [93]
HCV	DLBCL	Yes [93]
B. afzelii	Cutaneous MALT	Yes [103]
B. burgdorferi	Cutaneous MZ, FL, DLBCL	

Table 2: Shows the infectious agents that have been studied in CBCL.

Viral Infection

EBV is a ubiquitous lymphotropic herpesvirus that infects >90% of the worldwide population, transforms human B-cells in vitro, ans is particularly associated with several B-cell lymphomas [57]. Among these subtypes, EBV-positive DLBCL NOS, lymphomatoid granulomatosis, EBV+ mucocutaneous ulcer, and plasmablastic lymphoma primarily the skin [93].

EBV-positive DLBCL, NOS is an EBV-associated B-cell lymphoma that occurs mostly in elderly patients without any immunodeficiencies [94]. Jung, et al. [95] recently demonstrated that patients with primary cutaneous EBV-positive DLBCL-NOS are older than patients with cutaneous EBV-negative DLBCL-leg type. Nonnodular lesions predominated in primary cutaneous EBV-positive DLBCL-NOS rather than in EBV-negative DLBCL-leg type. Stage T3 lesions are less frequent in primary cutaneous EBV-positive DLBCL-NOS. Primary cutaneous EBV-positive DLBCL-NOS tend to have worse overall survival than EBV-negative DLBCL-leg type. The authors found no difference in overall survival between patients with primary cutaneous disease and concurrent skin and extracutaneous disease.

Cutaneous manifestations of EBV-driven B-cell lymphoid proliferations do not usually because of severe immunodeficiency. Few cases of extranodal EBV-associated B-cell lymphomas emerging in patients with angioimmunoblastic T-cell lymphoma (AITL) have been published, scarcely with a cutaneous presentation [96].

Finally, HIV, KSHV/HHV8 and hepatitis C virus (HCV) have been associated with DLBCL, including plasmablastic lymphoma [92].

Bacterial Infection

Borrelia burgdorferi infection associated with indolent lymphomas such as cutaneous MZL and follicular lymphoma, and with aggressive lymphomas such as DLBCL with cutaneous localization and mantle cell lymphoma has been reported [13].

In biopsies of patients with cutaneous MALT lymphomas from Europe and Australia, as well as in tissue samples from patients with FL and DLBCL, DNA of *Borrelia burgdorferi* has been detected [78,97]. Moreover, regression of infiltrative lesions following antibiotic treatment, mainly cephalosporin and tetracycline, was observed in patients with low-stage cutaneous MALT lymphoma [13,98]. Based on these results, oral antibiotics have been accepted as first-line treatment [99].

Borrelia infection may conduct to the formation of atypical lymphoid follicles in the skin, and lymphocytes may additionally infiltrate the dermis producing borrelial "lymphocytoma" which can be hard to distinguish histologically from MZL [3]. Some reports show that persistent inflammation throughout Borrelia infection may lead to monoclonal B-cell proliferation and BCL-2 protein expression [100,101]. Cutaneous MALT seems to be associated with *Borrelia afzelii* [102]. The role of other Borrelia species in the development of B-cell lymphoma is still arguable.

Contrastingly, Papadopoulou, et al. [14] have recently published a study and meta-analysis on the role of *Borrelia burgdorferi* in cutaneous CBCL in an endemic area, using highly sensitive Borrelia PCR assays for detection. The investigators did not find any association between Borrelial infection and CBCL. Their own meta-analysis of all CBCL reported in the literature related to Borrelia had an odds ratio <1. These results reinforce the need to look other pathogenetic factors that could be involved in the development of CBCL.

An association between Borrelia infection and cutaneous B-cell lymphoma was conducted before standardization of molecular techniques for lymphoma diagnosis. In the differential diagnosis of Borrelia lymphocytoma and cutaneous B-cell lymphoma, especially of the MZL type, the application of Borrelia PCR in the case of a dense T-cell-rich B-lymphocytic infiltrate is important. In order to avoid antibiotic resistance, antibiotic therapy should be strictly considered in the absence of pathogen detection.

Conclusions

The involvement of infectious agents in cutaneous lymphoproliferative disorders remains an open topic. Interestingly, infectious agents such as HTLV-1, EBV, HIV

and HCV, have been shown to be potential oncogenes in the development of NHL. However, in PCL only EBV and *S. aureus* have shown to be associated mainly with CBCL and CTCL, respectively, while studies have controversial results on the role of *Borrelia burgdorferi* in PCL. Therefore, antibiotic therapy should be carefully considered in the absence of pathogen detection to prevent antibiotic resistance. Host and tumor genomics, and in vitro studies may be important to suggest other factors concerning the pathogenesis of lymphoma development and progression.

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References

1. Fujii K (2022) Pathogenesis of cutaneous T cell lymphoma: Involvement of Staphylococcus aureus. J Dermatol 49(2): 202-209.

2. Groves FD, Linet MS, Travis LB, Devesa SS (2000) Cancer surveillance series : non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 92: 1240-1251.

3. Biernat MM, Wróbel T (2021) Bacterial infection and non-Hodgkin B-cell lymphoma: interactions between pathogen, host and tumor environment. Int J Mol Sci 22(14): 7372.

4. Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, et al. (2019) The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 133(16): 1703-1714.

5. Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, et al. (2019) British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Br J Dermatol 180(3): 496-526.

6. D'Agostino P, Kent A, Sharp E, Schmidt F, Turini M (2020) Mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) epidemiology and treatment pathway in Spain: new insights for an accurate description. Drugs Context 9: 2020-4-8.

7. Elmasry MF, Youssef R, Elbendary A, Helmy K, Abdelkader HA (2021) Cutaneous lymphomas and COVID-19: what is known so far? Dermatologic Therapy 34: e14463.

8. Durgin JS, Weiner DM, Wysocka M, Rook AH (2021) The immunopathogenesis and immunotherapy of cutaneous T cell lymphoma: part I, pathways and targets for immune restoration and tumor eradication. J Am Acad Dermatol 84(3): 587-595.

9. Mirvish ED, Pomerantz RG, Geskin LJ (2011) Infectious agents in cutaneous T-cell lymphoma. J Am Acad Dermatol 64(2): 423-431.

10. Ferreri AJ, Ernberg I, Copie-Bergman C (2009) Infectious agents and lymphoma development: molecular and clinical aspects. J Intern Med 265: 421-438.

11. Song S, Vuai MS, Zhong M (2018) The role of bacteria in cancer therapy – enemies in the past, but allies at present. Infect Agent Cancer 13: 9.

12. Stevens WB, Netea MG, Kater AP, van der Velden WJ (2016) Trained immunity: consequences for lymphoid malignancies. Haematologica 101(12): 1460-1468.

13. Travaglino A, Varricchio S, Pace M, Russo D, Picardi M, et al. (2018) *Borrelia burgdorferi* in primary cutaneous lymphomas: a systematic review and meta-analysis. J Dtsch Dermatol Ges 18(12): 1379-1384.

14. Papadopoulou K, Falk TM, Metze D, Böer-Auer A (2022) No evidence of Borrelia in cutaneous infiltrates of B-cell lymphomas with a highly sensitive, semi-nested real-time polymerase chain reaction targeting the 5S-23S intergenic spacer region. J Eur Acad Dermatol Venereol 36(6): 836-845.

15. Axelrod PI, Lorber B, Vonderheid EC (1992) Infections complicating mycosis fungoides and Sézary syndrome. JAMA 267(10): 1354-1358.

16. Lee J, Richardson SK, Melhem ER, Rook AH, Kim EJ (2007) Progressive multifocal leukoencephalopathy from JC virus in a patient with advanced mycosis fungoides. J Am Acad Dermatol 57(5): 893-5.

17. Suga H, Sugaya M, Miyagaki T, Ohmatsu H, Kawaguchi M, et al. (2014) Skin barrier dysfunction and low antimicrobial peptide expression in cutaneous T-cell lymphoma. Clin Cancer Res 20(16): 4339-4348.

18. Yazdanparast T, Yazdani K, Ahmad Nasrollahi S, Izadi Firouzabadi L, Humbert P, et al. (2021) Biophysical and ultrasonographic changes in early patch/plaque stage of mycosis fungoides, compared with uninvolved skin. Skin Res Technol 27: 1034.

19. Wolk K, Mitsui H, Witte K, Gellrich S, Gulati N, et al.

(2014) Deficient cutaneous antibacterial competence in cutaneous T-cell lymphomas: role of Th2-mediated biased Th17 function. Clin Cancer Res 20(21): 5507-5516.

20. Yawalkar N, Ferenczi K, Jones DA, Yamanaka K, Suh KY, et al. (2013) Profound loss of T-cell receptor repertoire complexity in cutaneous T-cell lymphoma. Blood 102(12): 4059-4066.

21. Ghazawi FM, Alghazawi N, Le M, Netchiporouk E, Glassman SJ, et al. (2019) Environmental and other extrinsic risk factors contributing to the pathogenesis of cutaneous T cell lymphoma (CTCL). Front Oncol 9: 300.

22. Tsambiras PE, Patel S, Greene JN, Sandin RL, Vincent AL (2001) Infectious complications of cutaneous T-cell lymphoma. Cancer Control 8(2): 185-188.

23. Kim EJ, Hess S, Richardson SK, Newton S, Showe LC, et al. (2005) Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest 115(4): 798-812.

24. Jackow CM, Cather JC, Hearne V, Asano AT, Musser JM, et al. (1997) Association of erythrodermic cutaneous T-cell lymphoma, superantigen-positive staphylococcus aureus, and oligoclonal T-cell receptor Vbeta gene expansion. Blood 89(1): 32-40.

25. Willerslev-Olsen A, Krejsgaard T, Lindahl LM, Litvinov IV, Fredholm S, et al. (2016) Staphylococcal enterotoxin A (SEA) stimulates STAT3 activation and IL-17 expression in cutaneous T-cell lymphoma. Blood 127(10): 1287-1296.

26. Willerslev-Olsen A, Buus TB, Nastasi C, Blümel E, Gluud M, et al. (2020) Staphylococcus aureus enterotoxins induce FOXP3 in neoplastic T cells in Sézary syndrome. Blood Cancer J 10(5): 1-11.

27. Kopp KL, Ralfkiaer U, Gjerdrum LM, Helvad R, Pedersen IH, et al. (2013) STAT5-mediated expression of oncogenic miR-155 in cutaneous T-cell lymphoma. Cell Cycle 12(12): 1939-1947.

28. Thomas D, Dauwalder O, Brun V, Badiou C, Ferry T, et al. (2009) Staphylococcus aureus superantigens elicit redundant and extensive human Vbeta patterns. Infect Immun 77(5): 2043-2050.

29. Woetmann A, Lovato P, Eriksen KW, Krejsgaard T, Labuda T, et al. (2007) Nonmalignant T cells stimulate growth of T-cell lymphoma cells in the presence of bacterial toxins. Blood 109(8): 3325-3332.

30. Blümel E, Munir Ahmad S, Nastasi C, Willerslev-Olsen A, Gluud M, et al. (2020) Staphylococcus aureus alpha-toxin inhibits CD8 T cell-mediated killing of cancer cells in cutaneous T-cell lymphoma. OncoImmunology 9(1): 1751561.

31. Fierro MT, Cuffini AM, Novelli M, Banche G, Allizond V, et al. (2011) Functional and phenotypical alterations of polymorphonuclear cells in Sézary syndrome patients. Eur J Dermatol 21(6): 921-929.

32. Ravat FE, Spittle MF, Russell-Jones R (2006) Primary cutaneous T-cell lymphoma occurring after organ transplantation. J Am Acad Dermatol 54(4): 668-675.

33. Martinez-Escala ME, Posligua AL, Wickless H, Rutherford A, Sable KA, et al. (2018) Progression of undiagnosed cutaneous lymphoma after anti-tumor necrosis factor-alpha therapy. J Am Acad Dermatol 78(6): 1068-1076.

34. Zackheim HS, Koo J, LeBoit PE, McCalmont TH, Bowman PH, Kashani-Sabet M, et al. (2002) Psoriasiform mycosis fungoides with fatal outcome after treatment with cyclosporine. J Am Acad Dermatol 47(1): 155-157.

35. Espinosa ML, Nguyen MT, Aguirre AS, Martinez-Escala ME, Kim J, et al. (2020) Progression of cutaneous T-cell lymphoma after dupilumab: case review of 7 patients. J Am Acad Dermatol 83(1): 197-199.

36. Willerslev-Olsen A, Krejsgaard T, Lindahl LM, Bonefeld CM, Wasik MA, et al. (2013) Bacterial toxins fuel disease progression in cutaneous T-cell lymphoma. Toxins (Basel) 5(8): 1402-1421.

37. MacKie RM (1981) Initial event in mycosis fungoides of the skin is viral infection of epidermal Langerhans cells. Lancet 2: 283-285.

38. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, et al. (1980) Detection and isolation of type c retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA 77(12): 7415-7419.

39. Abrams JT, Balin BJ, Vonderheid EC (2001) Association between Sézary T-cell activating factor, Chlamydia pneumoniae and cutaneous T-cell lymphoma. Ann NY Aca Sci 941: 69-85.

40. Rössler MJ, Rappl G, Muche M, Hasselmann DO, Sterry W, et al. (2003) No evidence of skin infection with Chlamydia pneumoniae in patients with cutaneous T-cell lymphoma. Clin Microbiol Infect 9(7): 721-723.

41. Dulmage BO, Feng H, Mirvish E, Geskin L (2015) Black cat in a dark room: absence of a directly oncogenic virus does not eliminate the role of an infectious agent in CTCL pathogenesis. Br J Dermatol 172(5): 1449-1451.

42. Sadler AJ, Williams BR (2007) Structure and function of the protein kinase R. Curr Top Microbiol Immunol 316: 253-292.

43. van der Loo EM, van Muijen GN, van Vloten WA, Beens W, Scheffer E, et al. (1979) C-type virus-like particles specifically localized in Langerhans cells and related cells of skin and lymph nodes of patients with mycosis fungoides and Sézary's syndrome: a morphological and biochemical study. Virchows Arch B Cell Pathol Incl Mol Pathol 31(2): 193-203.

44. Manzari V, Gismondi A, Barillari G, Morrone S, Modesti A, et al. (1987) HTLV-V: a new human retrovirus isolated in a Tac-negative T-cell lymphoma/leukemia. Science 238(4833): 1581-1583.

45. Zucker-Franklin D, Coutavas EE, Rush MG, Zouzias DC (1991) Detection of human T-lymphotropic virus-like particles in cultures of peripheral blood lymphocytes from patients with mycosis fungoides. Proc Natl Acad Sci USA 88(17): 7630-7634.

46. Zucker-Franklin D, Hooper WC, Evatt BL (1992) Human lymphotropic retroviruses associated with mycosis fungoides: evidence that human T-cell lymphotropic virus type II (HTLV-II) as well as HTLV-I may play a role in the disease. Blood 80(6): 1537-1545.

47. Bazarbachi A, Soriano V, Pawson R, Vallejo A, Moudgil T, et al. (1997) Mycosis fungoides and Sézary syndrome are not associated with HTLV-I infection:; an international study. Br J Haematol 98(4): 927-933.

48. Pawlaczyk M, Filas V, Sobieska M, Gozdzicka-Józefiak A, Wiktorowicz K, et al. (2005) No evidence of HTLV-I infection in patients with mycosis fungoides and Sézary syndrome. Neoplasma 52(1): 52-55.

49. Tan RS, Butterworth CM, McLaughlin H, Malka S, Samman PD, et al. (1974) Mycosis fungoides – a disease of antigen persistence. Br J Dermatol 91: 607-616.

50. Kaplan MH, Kaminski M, Estes JM, Gitlin SD, Zahn J, et al. (2019) Structural variation of centromeric endogenous retroviruses in human populations and their impact on cutaneous T-cell lymphoma, Sézary syndrome , and HIV infection. BMC Med Genomics 12(1): 58.

51. Kempf W, Kadin ME, Dvorak AM, Lord CC, Burg G, et al. (2003) Endogenous retroviral elements, but not exogenous retroviruses, are detected in CD30-positive lymphoproliferative disorders of the skin. Carcinogenesis 24(2): 301-306.

52. Erkek E, Sahin S, Atakan N, Kocagöz T, Olut A, et al. (2001) Examination of mycosis fungoides for the presence of Epstein-Barr virus and human herpes virus-6 by polymerase chain reaction. J Eur Acad Dermatol Venerol 15(5): 422-426.

53. Nagore E, Ledesma E, Collado C, Oliver V, Pérez-Pérez A, et al. (2000) Detection of Epstein-Barr virus and humanherpesvirus 7 and 8 genomes in primary cutaneous T- and B-cell lymphomas. Br J Dermatol 143(2): 320-323.

54. Shimakage M, Sasagawa T, Kawahara K, Yutsudo M, Kusuoka H, et al. (2001) Expression of Epstein-Barr virus in cutaneous T-ecll lymphoma including mycosis fungoides. Int J Cancer 92(2): 226-231.

55. Kreuter A, Bischoff S, Skrygan M, Wieland U, Brockmeyer NH, et al. (2008) High association of human herpesvirus 8 in large-plaque parapsoriasis and mycosis fungoides. Arch Dermatol 144(8): 1011-1016.

56. Takata K, Hong ME, Sitthinamsuwan P, Loong F, Tan SY, et al. (2015) Primary cutaneous NK/T-cell lymphoma, nasal type and CD56-positive peripheral T-cell lymphoma: a cellular lineage and clinicopathological study of 60 patients from Asia. Am J Surg Pathol 39(1): 1-12.

57. Gru AA, Jaffe ES (2017) Cutaneous EBV-related lymphoproliferative disorders. Semin Diagn Pathol 34(1): 60-75.

58. Trento E, Castilletti C, Ferraro C, Lesnoni La Parola I, Mussi A, et al. (2005) Human herpesvirus 8 infection in patients with cutaneous lymphoproliferative diseases. Arch Dermatol 141(10): 1235-1242.

59. Henghold WB 2nd, Purvis SF, Schaffer J, Giam CZ, Wood GS (1997) No evidence of KSHV/HHV-8 in mycosis fungoides or associated disorders. J Invest Dermatol 108(6): 920-922.

60. Ponti R, Bergallo M, Costa C, Quaglino P, Fierro MT, et al. (2008) Human herpesvirus 7 detection by quantitative real time polymerase chain reaction in primary cutaneous T-cell lymphomas and healthy subjects: lack of a pathogenic role. Br J Dermatol 159(5): 1131-1137.

61. Berneman ZN, Torelli G, Luppi M, Jarrett RF (1998) Absence of a directly causative role for human herpesvirus 7 in human lymphoma and a review of human herpesvirus 6 in human malignancy. Ann Hematol 77(6): 275-278.

62. Herne KL, Talpur R, Breuer-McHam J, Champlin R, Duvic M (2003) Cytomegalovirus seropositivity is significantly associated with mycosis fungoides and Sézary syndrome.

Blood 101(6): 2132-2136.

63. Gupta RK, Ramble J, Tong CY, Whittaker S, MacMahon E (2006) Cytomegalovirus seroprevalence is not higher in patients with mycosis fungoides/Sézary syndrome. Blood 107(3): 1241-1242.

64. Bergallo M, Daprà V, Fava P, Ponti R, Calvi C, et al. (2018) DNA from human polyomaviruses, MWPyV, HPyV6, HPyV7, HPyV9 and HPyV12 in cutaneous T-cell lymphomas. Anticancer Res 38(7): 4111-411.

65. Phan TG, Dreno B, da Costa AC, Li L, Orlandi P, et al. (2016) A new protoparvovirus in human fecal samples and cutaneous T cell lymphomas (mycosis fungoides). Virology 496: 299-305.

66. Kreuter A, Nasserani N, Tigges C, Oellig F, Silling S, et al. (2018) Cutavirus infection in primary cutaneous B- and T-cell lymphoma. JAMA Dermatol 154(8): 965-967.

67. Emge DA, Bassett RL, Duvic M, Huen AO (2020) Methicillin-resistant Staphylococcus aureus (MRSA) is an important pathogen in erythrodermic cutaneous T-cell lymphoma (CTCL) patients. Arch Dermatol Res 312(4): 283-288.

68. Willerslev-Olsen A, Gjerdrum LMR, Lindahl LM, Buus TB, Pallesen EMH, et al. (2021) Staphylococcus aureus induces signal transducer and activator of transcription 5-dependent miR-155 expression in cutaneous T-cell lymphoma. J Invest Dermatol 141(10): 2449-2458.

69. Lindahl LM, Willerslev-Olsen A, Gjerdrum LMR, Nielsen PR, Blümel E, et al. (2019) Antibiotics inhibit tumor and disease activity in cutaneous T-cell lymphoma. Blood 134(13): 1072-1083.

70. Salava A, Deptula P, Lyyski A, Laine P, Paulin L, et al. (2020) Skin microbiome in cutaneous T-cell lymphoma by 16S and whole-genome shotgun sequencing. J Invest Dermatol 140(11): 2304-2308.

71. Harkins CP, MacGibeny MA, Thompson K, Bubic B, Huang X, et al. (2021) Cutaneous T-cell lymphoma skin microbiome is characterized by shifts in certain commensal bacteria but not viruses when compared with healthy controls. J Invest Dermatol 141(6): 1604-1608.

72. Lindahl LM, Iversen L, Ødum N, Kilian M (2022) Staphylococcus aureus and antibiotics in cutaneous T-cell lymphoma. Dermatology 238: 551-553.

73. Stanek G, Strle F (2003) Lyme borreliosis. Lancet 362(9396): 1639-1647.

74. Ponzoni M, Ferreri AJ, Mappa S, Pasini E, Govi S, et al. (2011) Prevalence of *Borrelia burgdorferi* infection in a series of 98 primary cutaneous lymphomas. Oncologist 16(11): 1582-1588.

75. Stinco G, Ruscio M, Bergamo S, Trotter D, Patrone P (2014) Clinical features of 705 *Borrelia burgdorferi* seropositive patients in an endemic area of northern Italy. ScientificWorldJournal 2014: 414505.

76. Cairns V, Wallenhorst C, Rietbrock S, Martinez C (2019) Incidence of Lyme disease in the UK: a population-based cohort study. BMJ Open 9(7): e025916.

77. Vandekerckhove O, De Buck E, Van Wijngaerden E (2021) Lyme disease in Western Europe: an emerging problem? A systematic review. Acta Clin Belg 76(3): 244-252.

78. Ferreri AJ, Govi S, Ponzoni M (2013) Marginal zone lymphomas and infectious agents. Semin Cancer Biol 23(6): 431-440.

79. Sukswai N, Lyapichev K, Khoury JD, Medeiros LJ (2020) Diffuse large B-cell lymphoma variants: an update. Pathology 52(1): 53-67.

80. Hennessy BT, Hanrahan EO, Daly PA (2004) Non-Hodgkin lymphoma: an update. Lancet Oncol 5(6): 341-353.

81. Pagano JS, Blaser M, Buendia MA, Damania B, Khalili K, et al. (2004) Infectious agents and cancer criteria for a causal relation. Semin Cancer Biol 14(6): 454-471.

82. Küppers R, Klein U, Hansmann ML, Rajewsky K (1999) Cellular origin of human B-cell lymphomas. N Engl J Med 341(20): 1520-1529.

83. Shaffer AL, Rosenwald A, Staudt LM (2002) Lymphoid malignancies: the dark side of B-cell differentiation. Nat Rev Immunol 2(12): 920-932.

84. Carbone A (2003) Emerging pathways in the development of AIDS-related lymphomas. Lancet Oncol 4(1): 22-29.

85. Bower M (2002) The management of lymphoma in the immunosuppressed patient. Best Pract Res Clin Haematol 15(3): 517-532.

86. Seto M (2004) Genetic and epigenetic factors involved in B-cell lymphomagenesis. Cancer Sci 95(9): 704-710.

87. Okano M (2000) Haematological associations of Epstein-Barr virus infection. Baillières Best Pract Res Clin Haematol 13(2): 199-214.

88. Boshoff C, Weiss R (2002) AIDS-related malignancies.

Nat Rev Cancer 2: 373-382.

89. Bazarbachi A, Ghez D, Lepelletier Y, Nasr R, de Thé H, et al. (2004) New therapeutic approaches for adult T-cell leukaemia. Lancet Oncol 5(11): 664-672.

90. Cavalli F, Isaacson PG, Gascoyne RD, Zucca E (2001) MALT lymphomas. Hematology Am Soc Hematol Educ Program 2001: 241-258.

91. Morse HC 3rd, Kearney JF, Isaacson PG, Carroll M, Fredrickson TN, et al. (2001) Cells of the marginal zone: origins, function and neoplasia. Leuk Res 25(2): 169-178.

92. Suarez F, Lortholary O, Hermine O, Lecuit M (2006) Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation. Blood 107(8): 3034-3044.

93. Mo XL, Zhou MY, Ye QR (2020) Primary cutaneous Epstein-Barr virus positive diffuse large B-cell lymphoma, not otherwise specified, in a nonimmunocompromised young man: a case report. J Cutan Pathol 47(4): 387-389.

94. Vermeesch J, Ramirez J, Lafond A (2018) Primary cutaneous Epstein-Barr virus-positive diffuse large B-cell lymphoma: a rare and aggressive cutaneous lymphoma. Cutis 102(6): 421-424.

95. Jung JM, Na HM, Won CH, Chang SE, Lee MW, et al. (2022) Cutaneous Epstein-Barr virus-positive diffuse large B-cell lymphoma, not otherwise specified: a systematic review and comparative analysis with Epstein-Barr virus-negative, leg type. J Am Acad Dermatol 86(1): 221-225.

96. Poon F, Ieremia E, Collins G, Matin RN (2019) Epstein-Barr virus-induced cutaneous diffuse large B-cell lymphoma in a patient with angioimmunoblastic T-cell lymphoma. Am J Dermatopathol 41(12): 927-930.

97. Melenotte C, Mezouar S, Mège JL, Gorvel JP, Kroemer G, et al. (2020) Bacterial infection and non-Hodgkin's lymphoma. Crit Rev Microbiol 46(3): 270-287.

98. Raderer M, Kiesewetter B, Ferreri AJ (2016) Clinicopathologic characteristics and treatment of marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). CA Cancer J Clin 66(2): 153-171.

99. Sriskandarajah P, Dearden CE (2017) Epidemiology and environmental aspects of marginal zone lymphomas. Best Pract Res Clin Haematol 30(1-2): 84-91.

100. Leinweber B, Colli C, Chott A, Kerl H, Cerroni L (2004) Differential diagnosis of cutaneous infiltrates of B lymphocytes with follicular growth pattern. Am J Dermatopathol 26(1): 4-13.

101. Colli C, Leinweber B, Müllegger R, Chott A, Kerl H, et al. (2004) *Borrelia burgdorferi*-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases. J Cutan Pathol 31(3): 232-240.

102. Aberer E, Fingerle V, Wutte N, Fink-Puches R, Cerroni L (2011) Within European margins. Lancet 377(9760): 178.