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Infectious agents in cutaneous T-cell lymphoma

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Abstract

Infectious agents have long been suspected as potential causative agents in cutaneous T-cell lymphoma (CTCL). Tissues of patients with CTCL have been evaluated for evidence of infection with a number of agents, including *Staphylococcus aureus*, retroviruses, and herpesviruses. These studies have failed to reveal a consistent association of CTCL with investigated agents. However, there is substantial evidence suggesting a potential role of a yet unidentified virus in CTCL. This article will review the findings of studies exploring potential roles of infectious agents in CTCL. In addition, we investigated CTCL tissues for evidence of infection with Merkel cell polyomavirus, a novel polyomavirus that was recently discovered as a probable carcinogenic agent in Merkel cell carcinoma. Cutaneous lesions demonstrating mycosis fungoides were stained with a monoclonal antibody against the Merkel cell polyomavirus T antigen, along with appropriate positive and negative controls. Immunohistochemical stains produced negative results in all examined mycosis fungoides specimens. These findings, which suggest a lack of association of CTCL with Merkel cell polyomavirus, add to the current body of knowledge regarding infectious agents and CTCL.

Keywords

cutaneous T-cell lymphoma; Epstein-Barr virus; herpesvirus; human T-lymphotrophic virus; infection; Merkel cell polyomavirus; retrovirus

Cutaneous T-cell lymphoma (CTCL) is a malignancy of T lymphocytes, generally of CD4⁺ immunophenotype, which home to the skin. The two major variants within the CTCL spectrum are mycosis fungoides (MF), characterized clinically by the development of patches, plaques, and tumors, and Sézary syndrome (SS), characterized by leukemic involvement. CTCL is the second most common extranodal non-Hodgkin lymphoma, and its origin is unknown. This article will review the findings of studies exploring potential roles of infectious agents, including *Staphylococcus aureus*, retroviruses, and herpesviruses, in CTCL. Original data suggesting a lack of association with the newly discovered Merkel cell polyomavirus (MCV) will then be presented.

A number of cancers are known to be caused by infectious agents. Some such agents trigger carcinogenesis indirectly, by producing states of chronic infection and inflammation. For instance, *Helicobacter pylori* can act as an indirect carcinogen leading to gastric cancer, and hepatitis B and C viruses may serve as indirect carcinogens in the development of hepatocellular carcinoma. Alternatively, infectious agents such as human papillomaviruses and Epstein-Barr virus (EBV) may cause oncogenesis by direct mechanisms, exerting

mutagenic effects that lead to malignant transformation. Causative roles have been posited for a number of infectious agents in CTCL, with hypotheses including both indirect and direct carcinogenic models of disease pathogenesis.

EVIDENCE FOR AN INFECTIOUS CAUSE OF CTCL

Early epidemiologic studies suggested associations of CTCL with industrial exposures,¹ suggesting the role of environmental factors in triggering disease carcinogenesis. Subsequent case-control studies designed to explore such hypotheses have yielded mixed results. Some have failed to provide evidence for relationships between occupational, recreational, or chemical exposure history and development of CTCL.²⁻⁴ In contrast, a multicenter European study showed that employment in the paper, glass, pottery, and ceramics industries⁵ and occupational exposure to halogenated hydrocarbons⁶ were associated with increased MF risk. However, such investigations have been difficult to execute and are complicated by the low prevalence of CTCL. Importantly, these studies were limited by simultaneous testing of a broad array of statistical hypotheses on a single data set, imparting a high likelihood that some apparently significant associations were a result of chance rather than a true biologic relationship. Hypothesis-driven confirmatory studies are needed.

Other epidemiologic findings are suggestive of an infectious origin. CTCL incidence is highest in the elderly,⁷ and the disease confers a higher risk of mortality in elderly patients.⁸ In addition, CTCL occurs more commonly than expected in immune-suppressed patients. It has been described after organ transplantation, and has an unusually aggressive course in these patients.⁹ A number of CTCL cases have been described in the setting of HIV.¹⁰ Wilkins et al¹¹ have described a group of HIV-associated cutaneous lymphoproliferative disorders closely resembling CTCL that occur primarily in patients with advanced HIV infection. A recent population-based study examining selected geographic areas in the United States found the highest CTCL incidence rate in San Francisco, CA, and the lowest rate in Iowa,¹² corresponding to an approximately 50-fold higher rate of HIV/AIDS in San Francisco, CA, relative to Iowa.¹³

In addition to epidemiologic findings, biologic features of CTCL also point to the possibility of an infectious cause. Yawalkar et al¹⁴ reported a profound loss of diversity in the T-cell receptor (TCR) repertoire in CTCL, which was demonstrated in peripheral blood specimens from all late-stage patients and up to half of early-stage patients analyzed for the study. In a subsequent investigation by the same group, it was also shown that TCR excision circles, which form as a result of gene rearrangement in naive T cells and thus measure relative levels of naive-versus-expanded T cells, are decreased in patients with CTCL of all disease stages. This decrease was proportional to the loss of T-cell repertoire diversity as measured by TCR-V β CDR3 spectratyping, and suggests that in addition to the expanded malignant T cells, nonmalignant T-cell families may also be expanding in CTCL in response to the loss of other families of T cells.¹⁵ It is possible that specific T-cell families are subject to selective immunologic depletion or direct cytotoxic effects of a particular pathogen (similar to the reduction of CD4⁺ cells in HIV), resulting in the expansion of other T-cell families and the immunosuppressed phenotype observed in CTCL. Indeed, CTCL spectratyping profiles strongly resembled those of patients with HIV, which led Yawalkar et al¹⁴ to hypothesize that a T-cell tropic retrovirus could be involved in CTCL carcinogenesis.

Furthermore, the proliferation pattern of T cells in CTCL suggests an inciting role of a microbial superantigen. In contrast to the clonal pattern of expansion of neoplastic lymphocytes in other lymphomas, the malignant T-cell population in CTCL is oligoclonal, consisting of multiple distinct clones that share a common TCR-V β epitope.^{16,17}

Superantigens are the only agents known to stimulate polyclonal T-cell expansion in a $V\beta$ -restricted manner, and may be at work in the early stages of CTCL carcinogenesis.

Staphylococcus aureus

A pathogenic role of *S aureus* in CTCL has long been suspected. Patients with CTCL have a significantly higher rate of *S aureus* than the general population,^{18,19} and a relationship between staphylococcal sepsis and disease progression has been noted.²⁰ Treatment of *S aureus* with antibiotics alone may lead to significant improvement of colonized patients with MF.^{19,21} Although these data show an association of *S aureus* colonization with disease activity in CTCL, they do not imply a primary role of *S aureus* in triggering CTCL carcinogenesis.

As discussed above, it has been hypothesized that CTCL is driven by a superantigen-stimulated clonal proliferation of T cells. A number of studies provide evidence for the involvement of staphylococcal superantigens in CTCL pathogenesis. In vitro treatment of Sézary cells with staphylococcal exfoliating toxin and toxic shock syndrome toxin-1, toxins known to activate TCR- $V\beta 2$, led to selective proliferation of $V\beta 2.1^+$ Sézary cells while failing to stimulate $V\beta 2.1^-$ cells.²² In a prospective study of 42 patients with CTCL, Jackow et al²³ found that 76% of patients had positive staphylococcal cultures from either the skin or the blood. Among these were 6 patients colonized with a toxic shock syndrome toxin-1 positive *S aureus* strain, all of whom had overexpansion of TCR- $V\beta 2$ in skin, peripheral blood, or both. These findings support the hypothesis that staphylococcal toxins are a source of chronic antigenic stimulation and concomitant T-cell proliferation in CTCL.

Woetmann et al²⁴ reported that treatment with staphylococcal superantigens did not directly affect the growth of CTCL tumor cell lines, but instead induced robust proliferation of superantigen-responsive nonmalignant T cells in coculture; the nonmalignant T cells then stimulated expansion of the malignant cells in a superantigen- and major histocompatibility complex class II-dependent manner. This novel finding suggests that superantigen-induced expansion of malignant T cells relies on crosstalk between malignant and nonmalignant T-cell populations, rather than through a direct effect on the malignant cells.

Retroviruses—Van der Loo et al²⁵ observed retrovirus-like particles in Langerhans cells residing within the skin and lymph nodes of patients with MF and SS. This observation contributed to the hypothesis of MacKie²⁶ that viral infection of Langerhans cells is the initial event leading to CTCL carcinogenesis. The notion of retroviral involvement in CTCL was further propelled by the discovery of human T-lymphotrophic virus (HTLV), the retrovirus that causes adult T-cell leukemia and lymphoma. Because CTCL bears significant clinical and histopathological similarities to its nodal correlate, HTLV became a subject of close scrutiny as a putative causative factor of CTCL.

In a cell line derived from a patient with SS, Manzari et al²⁷ detected retrovirus-like particles and reverse transcriptase activity. The investigators isolated a novel retrovirus related to HTLV-I and HTLV-II, which they named HTLV-V. However, no subsequent data confirmed the existence of HTLV-V. In two later studies, Zucker-Franklin et al^{28,29} found HTLV-like inclusions in the peripheral blood mononuclear cells of patients with CTCL and HTLV proviral sequences and reverse transcriptase activity in some cell lines derived from peripheral blood mononuclear cells of patients with MF and SS. In the latter study, in which the lymphocytes of 9 patients with MF were cultured, one cell line showed polymerase chain reaction (PCR) amplification of HTLV-II gene sequences, suggesting a potential role of HTLV-II and HTLV-I in CTCL.

Two large subsequent studies failed to amplify HTLV genomic sequences in DNA extracted from skin lesions and peripheral blood mononuclear cells of patients with CTCL, or to detect anti-HTLV antibodies in patient sera.^{30,31} In an international study, Bazarbachi et al³⁰ analyzed 215 samples from MF, SS, lymphomatoid papulosis, and unspecified CTCL subtypes, whereas Pawlaczyk et al³¹ analyzed specimens from 47 Polish patients with MF and SS; in both studies, cutaneous lesions and serum samples were uniformly negative for HTLV-I DNA and anti-HTLV-I antibodies. Although these studies essentially rule out HTLV-I as the cause of CTCL, repeated observations of viruslike particles and reverse transcriptase activity in the peripheral blood of patients with CTCL suggest the possible involvement of an alternate retrovirus in CTCL. Findings have suggested, for instance, a correlation between human endogenous retrovirus–reactive antibody titer and CTCL disease severity.³² In addition, reverse transcriptase and human endogenous retrovirus transcripts—but not those of other retroviruses—have been detected in lymphomatoid papulosis, a subset of CTCL.³³ However, a causal relationship between any retrovirus and CTCL has yet to be established.

Herpesviruses—A number of viruses other than HTLV have been investigated in CTCL, with similarly mixed results. Significant work has focused on members of the herpesvirus family because of known associations of herpesviruses with other malignancies. CTCL tissues have been evaluated for evidence of infection with EBV,^{34–36} Kaposi sarcoma–associated herpesvirus (KSHV) (human herpesvirus [HHV]-8),^{35,37,38} HHV-6,³⁴ HHV-7,^{35,39,40} and cytomegalovirus (CMV).^{41,42}

Genomic sequences of EBV have been detected in CTCL lesional and blood samples, but not consistently. Erkek et al³⁴ amplified EBV DNA by PCR in 9 of 92 (9.8%) cutaneous lesions from patients with MF. Nagore et al³⁵ analyzed cutaneous lesions of patients with MF, pleomorphic small/medium CTCL, and angiocentric CTCL, finding that 12 of 36 (33%) tested samples amplified EBV DNA by PCR. Shimakage et al³⁶ showed high rates of positivity for EBV nucleic acids in a small sample of cutaneous lesions excised from patients with a variety of CTCL subtypes: 6 of 7 (86%) samples were positive for EBV DNA by PCR, whereas all tested samples had positive messenger RNA and DNA hybridization signals on in situ hybridization analysis. In contrast to these findings are those of a recent study by Kreuter et al,³⁸ in which MF cutaneous lesion samples were uniformly negative for EBV DNA and protein by real-time PCR and immunohistochemistry, respectively.

Trento et al⁴³ found a high prevalence of KSHV/HHV-8 infection in patients with large-plaque parapsoriasis, which is often considered to be a precursor lesion for CTCL. This finding led to analyses of CTCL tissues for evidence of KSHV/HHV-8 infection, despite previous reports that CTCL skin specimens were uniformly negative for KSHV/HHV-8 DNA by PCR and Southern blot.^{35,37} In the most recent study, 7 of 10 (70%) analyzed MF samples were positive for KSHV/HHV-8 DNA by PCR, but this finding could not be confirmed by immunohistochemistry in any of 31 tested MF samples.³⁸

Current data fail to support a role for HHV-6 and HHV-7 in CTCL pathogenesis. Only one of 92 (1%) cutaneous lesions from patients with MF were positive for HHV-6 DNA.³⁴ Between 0% and 18% of cutaneous lesions representing a variety of CTCL subtypes were positive for HHV-7 DNA in 3 separate studies.^{35,39,40}

CMV infection is common in T-cell–deficient populations such as HIV-positive patients and transplantation recipients on immunosuppressive regimen. Because of the functional T-cell deficiency in CTCL, the incidence of CMV seropositivity has been assessed in cohorts of patients with CTCL. Conflicting results have been reported: a retrospective analysis in 2003

found a significantly higher rate of CMV seropositivity in patients with MF and SS than in age-matched control subjects,⁴¹ whereas a subsequent study failed to replicate this finding.⁴²

Merkel cell polyomavirus—Recently, a novel polyomavirus was discovered as a probable carcinogenic agent in Merkel cell carcinoma (MCC). This virus, named “Merkel cell polyomavirus,” has also been isolated from normal-appearing skin, non-MCC skin tumors, and various other tissues. An association between MCV and CTCL has not been evaluated; we sought to determine whether MCV is present in CTCL tumors.

We analyzed cutaneous lesion samples from 4 patients with MF in accordance with an institutional review board–approved protocol. A tumor sample from a patient with MCC was used as a positive control.

The protocol for immunohistochemistry is as previously described.⁴⁴ In brief, formalin-fixed, paraffin-embedded biopsy specimens of MF lesions were cut onto slides. After deparaffinization and hydrogen peroxide treatment, heat-induced epitope retrieval was performed using EDTA antigen retrieval buffer (Dako, Carpinteria, CA) at 126°C for 30 minutes. After blocking with Protein Block (Dako), slides were incubated for 30 minutes with CM2B4, a monoclonal mouse antibody raised against the MCV T antigen (provided by Dr Yuan Chang), followed by Mouse EnVision Polymer (Dako) for 30 minutes. Reactions were developed with the Betazoid diaminobenzidine chromogen (Dako), and slides were counterstained with hematoxylin.

Immunohistochemical stains were negative for the MCV T antigen in all examined MF specimens (Fig 1), whereas the MCC specimen (positive control) showed strongly positive MCV findings (Fig 2). These results strongly suggest that MCV is not associated with CTCL pathogenesis, although they do not exclude that possibility.

SUMMARY

Previous studies evaluating CTCL specimens for nucleic acid and protein components of various viruses have yielded widely conflicting results (Table I). Possible explanations for these inconsistent findings include various forms of contamination (eg, viral genomic contamination of PCR reactions); misdiagnosis of virus-associated cancers (eg, adult T-cell leukemia/lymphoma) as CTCL; and the limitations of current molecular and immunologic diagnostic techniques, which may be unable to fully differentiate between the various disease subtypes collectively characterized as CTCL. Most studies have probed possible associations with retroviruses and herpesviruses. Our study evaluating MF tumors for evidence of the recently discovered MCV yielded negative findings. Biologic and epidemiologic features of CTCL suggest the involvement of an infectious agent; however, the origin of CTCL remains unknown. Further studies exploring both infectious and noninfectious hypotheses are needed.

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Abbreviations used

CMV cytomegalovirus

CTCL	cutaneous T-cell lymphoma
EBV	Epstein-Barr virus
HHV	human herpesvirus
HTLV	human T-lymphotrophic virus
KSHV	Kaposi sarcoma–associated herpesvirus
MCC	Merkel cell carcinoma
MCV	Merkel cell polyomavirus
MF	mycosis fungoides
PCR	polymerase chain reaction
SS	Sézary syndrome
TCR	T-cell receptor

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CAPSULE SUMMARY

- The involvement of an infectious agent in cutaneous T-cell lymphoma (CTCL) has long been suspected; however, the origin of CTCL remains unknown.
- Elucidating disease origin is important for the advancement of diagnostic and therapeutic approaches to CTCL.
- We review the findings of studies exploring potential roles of infectious agents in CTCL.
- In addition, we report original findings suggesting a lack of association of CTCL with Merkel cell polyomavirus.

Fig 1. Representative mycosis fungoides tumor sample demonstrating negative staining for Merkel cell polyomavirus. (Hematoxylin stain; original magnification: $\times 10$.)

Fig 2. Tumor sample from patient with Merkel cell carcinoma (positive control). Uniformly Merkel cell polyomavirus (MCV)-positive tumor infiltrate and MCV-negative stroma. (Hematoxylin stain; original magnification: $\times 10$.)

Table 1
Results of previous studies investigating viral associations with cutaneous T-cell lymphoma

Virus	Cancer(s) with known viral role	CTCL subtype; specimens analyzed	Method(s) for viral detection	Findings in CTCL specimens	Reference
HTLV-I	Adult T-cell leukemia and lymphoma	MF and SS; cultured peripheral blood lymphocytes and cutaneous lesions	EM, immunohistochemistry, and PCR	<ul style="list-style-type: none"> • 18/20 (90%) Cultures showed abundance of HTLV-I-like particles on EM • 3/6 (0%) Cultures positive for HTLV-I protein • 1/4 (25%) Skin samples positive for HTLV-I DNA • 3/9 (25%) Cultures positive for HTLV-I DNA • 4/9 (44%) Samples positive for HTLV-I DNA 	28
		MF; peripheral blood lymphocytes	PCR		29
		MF, SS, LyP, unspecified; cutaneous lesions, fresh PBMC, cultured PBMC	ELISA, Western blot, PCR, and RT assay	<ul style="list-style-type: none"> • 0/215 (0%) Samples (121 fresh PBMC, 26 cultured PBMC, 68 skin lesions) positive for HTLV-I DNA • 0/26 (0%) PBMC cultures positive for RT activity • 0/78 (0%) Patients seropositive for anti-HTLV-I antibodies 	30
		MF and SS; cutaneous lesions and serum samples	PCR and enzyme immunoassay for anti-HTLV-I IgG	<ul style="list-style-type: none"> • 0/47 (0%) Samples (fresh PBMC, cultured PBMC, skin lesions) positive for HTLV-I DNA • 0/46 (0%) Patients seropositive for anti-HTLV-I antibodies 	31
HTLV-II	None	MF; peripheral blood lymphocytes	PCR	<ul style="list-style-type: none"> • 1/9 (9.8%) Samples positive for HTLV-II DNA 	29
		MF, pleomorphic small/medium CTCL, and angiocentric CTCL; cutaneous lesions	PCR	<ul style="list-style-type: none"> • 7/29 (24%) MF samples positive for EBV DNA • 2/4 (50%) Pleomorphic small/medium CTCL samples positive for EBV DNA • 3/3 (100%) Angiocentric CTCL samples positive for EBV DNA 	35
		MF; cutaneous lesions	PCR	<ul style="list-style-type: none"> • 9/92 (9.8%) Samples positive for EBV DNA 	34
		MF, diffuse large T-cell lymphoma, pleomorphic T-cell lymphoma, angiocentric lymphoma, lipotrophic T-cell lymphoma, and unspecified; cutaneous lesions	mRNA in situ hybridization, DNA in situ hybridization, PCR	<ul style="list-style-type: none"> • 12/12 (100%) Samples had positive mRNA hybridization signals • 8/8 (100%) Samples had positive DNA hybridization signals • 6/7 (86%) Samples positive for EBV DNA 	36
EBV	Burkitt lymphoma, nasopharyngeal carcinoma	MF; cutaneous lesions	Real-time PCR and immunohistochemistry	<ul style="list-style-type: none"> • 0/10 (0%) MF samples positive for EBV DNA • 0/25 (0%) MF samples positive for EBV protein 	38
		MF and SS; serum samples	ELISA and MEIA assays for CMV IgG antibodies	<ul style="list-style-type: none"> • Increased incidence of CMV seropositivity in MF/SS: 113/116 (97.4%) Patients seropositive for CMV IgG, vs 757/1322 (57.3%) control subjects ($P = .001$) 	41
CMV	None	MF and SS; serum samples	ELISA and MEIA assays for CMV IgG antibodies	<ul style="list-style-type: none"> • No increased incidence of CMV seropositivity in MF/SS: 32/53 (60.4%) Patients seropositive for CMV IgG, vs 16/26 (61.5%) control subjects ($P = .92$) 	42

Virus	Cancer(s) with known viral role	CTCL subtype; specimens analyzed	Method(s) for viral detection	Findings in CTCL specimens	Reference
HHV-6	None	MF; cutaneous lesions	PCR	<ul style="list-style-type: none"> • 1/92 (1.1%) Samples positive for HHV-6 DNA 	34
HHV-7	None	MF and CD30 ⁺ large-cell CTCL; cutaneous lesions	PCR	<ul style="list-style-type: none"> • 6/33 (18%) Samples positive for HHV-7 DNA 	35
		SS, LyP, and MF; cutaneous lesions	Real-time PCR	<ul style="list-style-type: none"> • 21/148 (14.2%) Samples positive for HHV-7 DNA 	39
		MF and SS	Southern blot	<ul style="list-style-type: none"> • 0/11 (0%) Samples positive for HHV-7 DNA 	40
		MF, LyP, and primary cutaneous CD30 ⁺ large-cell lymphoma; cutaneous lesions	PCR and Southern blot	<ul style="list-style-type: none"> • 0/30 (0%) Samples positive for KSHV/HHV-8 DNA 	37
		MF and CD30 ⁺ large-cell CTCL; cutaneous lesions	PCR	<ul style="list-style-type: none"> • 0/33 (0%) Samples positive for KSHV/HHV-8 DNA 	35
KSHV; HHV-8	Kaposi sarcoma	MF and LyP; cutaneous lesions	PCR and immunohistochemistry	MF samples: <ul style="list-style-type: none"> • 7/10 (70%) MF samples positive for KSHV/HHV-8 DNA • 0/31 (0%) MF samples positive for KSHV/HHV-8 protein LyP samples: <ul style="list-style-type: none"> • 0/4 (0%) LyP samples positive for KSHV/HHV-8 DNA • 0/8 (0%) LyP samples positive for KSHV/HHV-8 protein 	38

CMV, Cytomegalovirus; *CTCL*, cutaneous T-cell lymphoma; *EBV*, Epstein-Barr virus; *ELISA*, enzyme-linked immunosorbent assay; *EM*, electron microscopy; *HHV*, human herpesvirus; *HTLV*, human T-lymphotrophic virus; *KSHV*, Kaposi sarcoma-associated herpesvirus; *LyP*, lymphomatoid papulosis; *MEIA*, membrane enzyme immunoassay; *MF*, mycosis fungoides; *mRNA*, messenger RNA; *PBMC*, peripheral blood mononuclear cells; *PCR*, polymerase chain reaction; *RT*, reverse transcriptase; *SS*, Sézary syndrome.