Infectious agents in cutaneous T-cell lymphoma

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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. (J Am Acad Dermatol 2011;64:423-31.)

Key words: 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.

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

EVIDENCE FOR AN INFECTIOUS CAUSE OF CTCL

Early epidemiologic studies suggested associations of CTCL with industrial exposures,[1] suggesting

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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 industries[5] and occupational exposure to halogenated hydrocarbons[6] 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.

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.

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 immunesuppressed 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 al[11] 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 al[14] 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-Vβ 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 al[14] 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-Vβ epitope.[16,17] Superantigens are the only agents known to stimulate polyclonal T-cell expansion in a Vβ-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