Infectious Agents Involved in Cutaneous Lymphoma Etiopathogenesis

Subjects: Virology

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Cutaneous T-cell lymphoma (CTCL) belongs to the heterogeneous group of primary cutaneous lymphomas (CLs), the second most common extranodal non-Hodgkin hematological malignancy. CTCL accounts for approximately 75% of all CLs. Infectious agents are known to induce cancers by acting in either direct or indirect ways. Direct carcinogenesis is exerted, e.g., by the oncogenic viruses (papillomaviruses, polyomaviruses, retroviruses, and herpesviruses, among others), which initiate infections leading, through direct virus-driven mechanisms, to malignant cell transformations. Indirect carcinogenesis is typically associated with chronic infections and inflammation. In CTCL, the malignant T-cell population consists of various clones that share a common TCR-Vß epitope, in contrast to the malignant T-lymphocyte clonal expansion characteristic of other lymphomas. Since the ability to initiate polyclonal T-cell expansion in a Vß-restricted manner is characteristic of pathogen-produced immunostimulatory molecules known as superantigens, it was proposed that in CTCL carcinogenesis a bacterial and/or viral superantigen might serve as the trigger of chronic antigen stimulation and excessive T-cell proliferation.

Keywords: cutaneous T-cell lymphoma ; infectious etiology ; Parvoviridae ; cutavirus

1. Bacterial Superantigens in CTCL

1.1. *Staphylococcus aureus*

A primary role of *S. aureus* in triggering CTCL carcinogenesis has not been proven so far. However, an association of CTCL clinical behavior with *S. aureus* colonization was noted. A trend towards higher antibiotic-sensitive *S. aureus* colonization was observed in CTCL patients in comparison with healthy control subjects, and colonization was suggested to be directly related to the body surface area of CTCL involvement [1]. Furthermore, a relationship between *S. aureus*-induced sepsis and lymphoma progression was found [2]. Conversely, treatment of infection with antibiotics was reported to lead to significant clinical improvement in *S. aureus*-colonized MF patients [3][4]. Based on the above, it was initially suggested that staphylococcal superantigens might be strongly and directly involved in CTCL pathogenesis. Indeed, the *S. aureus*-derived superantigen family of proteins is known to consist of at least 26 different paralogues that exert their activities by crosslinking the major histocompatibility complex (MHC) type II molecules with TCR-Vß, resulting in aberrant T-cell proliferation and proinflammatory cytokine release [5]. However, subsequent in vitro studies revealed that *S. aureus*-derived superantigens induce superantigen-responsive non-malignant T-cell proliferation rather than direct CTCL cell growth stimulation [6]. Staphylococcal infection-associated tumor cell expansion in CTCL therefore seems to rely on crosstalk between malignant and non-malignant T lymphocytes against the background of *S. aureus* superantigen-induced chronic antigen stimulation.

1.2. *Borrelia burgdorferi*

B. burgdorferi is another bacterial agent that was suspected to play a plausible role in CTCL etiology. *B. burgdorferi*-specific flagellin gene sequences were detected in approximately 18% of the MF cases registered in a Lyme disease-endemic area in northeastern Italy but were not detected in any of the healthy control biopsies [7]. This bacterial pathogen is known to affect the complement function by inactivating complement regulatory proteins [8]. Moreover, *B. burgdorferi* is capable of persisting at immunoprivileged sites [9] using various immune evasion mechanisms, including outer-membrane antigenic variations [10]. It was suggested that *B. burgdorferi*, in particular in Lyme disease-endemic areas where long-term persistence-prone strains prevail, might function as a co-factor in MF pathogenesis and lead, through long-lasting antigen stimulation, to the malignant accumulation of skin-homing CD4+ lymphocytes. However, while improvement after *B. burgdorferi*-directed specific antibiotic therapy was described in other lymphoma types [11], the causal link between *B. burgdorferi* and MF remains controversial.

1.3. *Chlamydia pneumoniae*

Abrams et al. speculated that there might be an association between *C. pneumoniae* infection and CTCL development. The authors identified an effector molecule originally designated as Sézary T cell-activating factor (SAF). SAF was defined as an inducer of interleukin-2 (IL-2) receptors on both normal and malignant T cells from SS patients. Despite the fact that SAF was produced by mitogen-stimulated peripheral blood mononuclear cells (PBMCs) from these patients, the authors failed to isolate the SAF-encoding gene from eukaryotic libraries. Since SAF activity was detected in the cytoplasm of SS-derived malignant cells, together with RNA-DNA complexes, it was suggested that this molecule was not of eukaryotic origin but was derived from a cytoplasmically replicating intracellular pathogen [12][13]. Indeed, using a panel of antichlamydial antibodies, immunoelectron microscopy, and Western blotting, the authors demonstrated that the majority of MF patients were positive for *Chlamydia* determinants. Furthermore, *C. pneumoniae* DNA was detected in skin and lymph node samples from MF and SS patients, respectively [13]. Interestingly, it was also shown that this bacterium might chronically infect normal keratinocytes, thus leading to the expansion of *C. pneumoniae*-specific skin-homing T lymphocytes and CTCL development. However, it has not been elucidated whether SAF is physically associated with the bacterium or produced during its life cycle. It cannot be excluded that SAF may be a eukaryotic product that tends to localize within bacterial inclusions. *C. pneumoniae*'s involvement in the etiopathogenesis of CTCL therefore remains controversial and needs further investigation.

2. Viral Superantigens in CTCL

In addition to the bacterial agents presented above, several viruses characterized by their ability to provide chronic immune stimulation have been studied for their potential involvement in CTCL development.

2.1. Retroviruses: Human T-Lymphotropic Virus (HTLV)

In the 1990s, the hypothesis arose that retroviral infection of skin- and lymph node-resident Langerhans cells might be the triggering event in CTCL development [14]. Retrovirus-like particles were indeed found in these cells [15], and in 1980, the first publication was released describing the detection and isolation of the causative agent of human adult T-cell leukemia and lymphoma (ATL), HTLV, from MF patient's PBMCs [16]. The HTLV etiology hypothesis was further strengthened by well-established significant clinical and histopathological similarities between CTCL and ATL and by several later discoveries. HTLV-specific sequences and reverse transcriptase activity were detected in a cell line derived from an SS patient [17] and in cultured PBMCs from CTCL patients [18][19]. In contrast to the above reports, which speak in favor of HTLV association with CTCL pathogenesis, other studies failed to amplify HTLV-specific sequences from skin lesion- and PBMC-derived CTCL patient DNA [20][21][22][23]. In one 2010 study, Bonin et al. analyzed 83 skin biopsies from MF patients in comparison with 83 healthy subjects' skin samples. HTLV-I-like genomic sequences were found in 41% of the MF cases. Surprisingly, the frequency of HTLV-I detection in the control biopsies was also substantial, raising doubt about the direct role of this virus in CTCL carcinogenesis [24].

2.2. Herpesviruses: Epstein–Barr Virus (EBV) and Cytomegalovirus (CMV)

These viruses are known for their characteristic capacity for long-term persistence through the establishment of latent infections. It was therefore speculated that both EBV and CMV might readily exert chronic antigen stimulation, leading to T-cell hyperproliferation. Indeed, EBV and CMV genomic sequences and seropositivity were reported to be present in CTCL samples by various studies [25][26][27][28]. However, these data could not be reproduced by other groups who failed to trace a link between either EBV or CMV and CTCL [29][30]. Similar inconsistencies accompanied attempts to link the Kaposi sarcoma-associated herpesvirus (KSHV or HHV-8) and human herpesviruses 6 and 7 (HHV-6 and HHV-7) to CTCL. While some groups could prove the prevalence of KSHV infection and the presence of virus-specific DNA in CTCL patient samples [31], others either observed a uniform negativity [26][32] or failed to immunohistochemically confirm polymerase chain reaction (PCR)-detected virus DNA positivity [29]. Only a small percentage, if any, of the tested samples were shown to be positive for HHV-6 or HHV-7 DNA [25][26][33][34], thus failing to support any significant role of these herpesviruses in CTCL pathogenesis.

Other viruses, namely the Merkel polyomavirus, which affects the skin and possibly causes Merkel cell carcinoma, were also suggested as CTCL-triggering/associated agents. The link between this virus and CTCL was nevertheless unquestionably rejected [35].

In this way, none of the bacterial or viral agents discussed above could show a convincingly consistent association with CTCL. Therefore, the infectious etiology of CTCL remained a matter of speculation for decades, until recently, when a

novel viral candidate was discovered in MF specimens (see below). Infectious agents of both bacterial and viral origin that have been associated or investigated for an association with CTCL so far are listed in **Table 1**.

Table 1. Infectious agents investigated for their association with CTCL pathogenesis.

Origin	Infectious Agent	Taxonomical Classification (Family)	References
Bacterial	***Staphylococcus aureus***	***Staphylococcaceae***	[1][2][3][4][5][6]
	Borrelia burgdorferi	***Borreliaceae***	[7][8][9][10][11]
	Chlamydia pneumoniae	***Chlamydiaceae***	[12][13]
Viral	**Human T-lymphotropic virus (HTLV)**	***Retroviridae***	[14][15][16][17][18][19][20][21][22][23][24]
	Epstein–Barr virus (EBV)	***Orthoherpesviridae***	[25][26][27][28][29][30]
	Human cytomegalovirus (CMV)	***Orthoherpesviridae***	[25][26][27][28][29][30]
	Kaposi sarcoma-associated herpesvirus (KSHV)	***Orthoherpesviridae***	[26][31][32]
	Human herpesviruses 6 and 7 (HHV-6 and HHV-7)	***Orthoherpesviridae***	[25][26][33][34]
	Merkel polyomavirus	***Polyomaviridae***	[35]
	Cutavirus (CutaV)	***Parvoviridae***	[36][37][38][39][40][41][42][43]

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