Human Pathogenic Virus–Associated Pseudolymphomas and Lymphomas with Primary Cutaneous Manifestation in Humans and Animals


The etiologic role of viruses in cutaneous lymphoproliferative disorders is still controversial. In benign cutaneous pseudolymphomas of the human skin, human T-cell leukemia/lymphoma virus (HTLV) type I (HTLV-I), varicella zoster virus, Epstein-Barr virus (EBV), and human herpesvirus (HHV) 6 (HHV-6) are the viruses most often identified, whereas in malignant lymphoproliferative human immunodeficiency virus type 1 (HIV-1), HTLV-I/II, and EBV are more common. Coinfections with more than one virus species have occurred in a number of cases. HHV-8 in association with a lymphoproliferative lesion appears to be indicative of a malignant cutaneous lymphoma rather than of pseudolymphoma. Negative results are of no diagnostic value because of the relatively low number of virus-positive cases: a considerable proportion of studies (with a large number of subjects) have documented virus-negative findings. Perhaps with the exception of HIV-1, findings of viral infections seem to indicate secondary rather than primary infections. Reports on animal models associated with human pathogenic viruses are scarce.

To many histopathologists cutaneous lymphoproliferative disorders are of bewildering complexity. In general, they may be divided into two groups: benign cutaneous pseudolymphomas and malignant cutaneous lymphomas.

Cutaneous pseudolymphomas are a nonhomogeneous group of benign hyperplastic lymphoproliferative reactions in the skin that clinically and/or histologically mimic cutaneous lymphoma. However, our review focuses on ailments resembling lymphoma histologically, whereas virus-associated diseases (ecthyma contagiosum, infectious mononucleosis, etc.) that only clinically imitate lymphomas of the skin were not considered. Two categories of cutaneous pseudolymphomas are known: cutaneous T-cell pseudolymphoma and cutaneous B-cell pseudolymphoma [1]. The term cutaneous pseudolymphoma is relegated to the position of an aide-mémoire and must not be considered a term for diagnosis [2]. However, although uncommon, virus-associated cutaneous pseudolymphoma does exist.

In past decades many efforts have been made to differentiate between cutaneous pseudolymphoma and cutaneous lymphoma [3], which is sometimes difficult but is crucial because of the severe therapeutic consequences. It is possible that human herpesvirus (HHV) 8 (HHV-8) and human T-cell leukemia/lymphoma virus (HTLV) type 5 (HTLV-V) can be detected in lymphomas but not in pseudolymphomas of the skin. This may help to distinguish these two ailments. It must be noted that because of the relatively low yield of virus-positive cases, negative results are of no diagnostic value.

The term cutaneous lymphoma encompasses a constellation of diseases with malignant clonal lymphocytes that initially occur in the skin. The majority (about 65%) of all cutaneous lymphomas must be considered T-cell lymphoma, whereas B-cell lymphomas account for a much smaller proportion (~25%), and unusual or rare manifestations or nosologic entities account for up to 10% of all primary lymphomas of the skin.

The role of human pathogenic viruses in cutaneous lymphoproliferative disorders has been extensively studied. Results of in vitro experiments are inconsistent, and reports on animal models associated with human pathogenic viruses are scarce. Herein we present a critical review of the current state of knowledge.
Virus Infection and Cutaneous Pseudolymphoma in Humans

RNA Viruses

Human Immunodeficiency Viruses

*Human immunodeficiency virus type 1 (HIV-1).* Pseudolymphomas of the skin can be seen in a small number of HIV-1-positive patients, e.g., in association with cutaneous borreliosis [4]. In 1998, Bachelez et al. described HIV-associated cutaneous pseudolymphomas with oligoclonal cytotoxic CD8+ T cells that were reactive with HIV-1 antigen (Gag, Pol, Env)—expressing target cells [5]. HIV-1 may thus play a role in the pathogenesis of these HIV-associated skin lesions (e.g., via an altered/hyperplastic immune response).

Human T-cell Leukemia/Lymphoma Viruses

*Human T-cell leukemia/lymphoma virus type 1 (HTLV-I).* In 1986, Wantzin et al. reported the appearance of antibodies to HTLV-I in the serum of Danish patients with lymphomatoid papulosis [6]. One year later, Thomsen et al. confirmed these results in a different journal [7]. It is not clear whether the subjects of these two publications from 1986 and 1987 overlap, but according to the respective ratio of HTLV-I-antibody-positive/HTLV-I-antibody-negative patients with lymphomatoid papulosis, HTLV-I does not seem to play a major role in the pathogenesis of lymphomatoid papulosis.

Other RNA viruses

The literature provides no information about the finding of RNA viruses other than HIV-1 and HTLV-I in cutaneous pseudolymphoma.

DNA Viruses

Herpesviruses

*Human herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).* In 1991, Sexton et al. reported cutaneous HSV infection clinically mimicking cutaneous pseudolymphoma [8]. Although immunoperoxidase staining for HSV-1/HSV-2 antibodies was positive for only one of the two patients, ultrastructural examination in both cases revealed viral particles consistent with herpesvirus.

An extensive literature search with regard to HSV-1 and HSV-2 leads to the conclusion that these viruses do not seem to play a major role in the pathogenesis of cutaneous pseudolymphoma.

*Human herpesvirus 3 (HHV-3; varicella zoster virus [VZV]).* Few reports describe cutaneous pseudolymphomas involving regions of prior VZV infection [9, 10]. However, in almost identical terms, the above-listed references implicate VZV as a possible etiologic agent [11]. It should not be forgotten that full-blown herpes zoster is seen primarily in patients with an impaired immune system. In such an environment, development of a pseudolymphoma may be facilitated. However, the role of VZV in the etiology of this group of lesions is not yet fully understood.

Review of the literature suggests that VZV does not seem to play a primary role in the pathogenesis of cutaneous pseudolymphomas but perhaps facilitates their outbreak in a few particular individuals.

*Human herpesvirus 4 (HHV-4; Epstein-Barr virus [EBV]).* Peris et al. were able to identify EBV DNA in some patients with cutaneous pseudolymphoma [12]. All cases were negative for small EBV-encoded nuclear RNAs (EBERs), suggesting a latent infection. Brice et al. did not find EBV genome in a case of lymphomatoid papulosis among the controls of a study on patients with cutaneous T-cell lymphoma [13].

Therapy may alter the results of virus detection experiments: results of EBV-antibody immunolabelling have been negative in cells [5]. HIV-1 may thus play a role in the pathogenesis of these cases of cutaneous pseudolymphoma associated with low-dose methotrexate treatment for rheumatoid arthritis [14].

Publications on EBV in cutaneous pseudolymphoma do not provide subtype (EBV-1, EBV-2, EBV-A, EBV-B)—specific information. This may be of some importance, since subtypes differ in tissue distribution as well as in antigenic structures that are often sought for (e.g., EBV-nuclear antigen-2 [EBNA-2] and late membrane protein [LMP]) [15]. Overall, EBV does not seem to play a major role in the pathogenesis of cutaneous pseudolymphoma.

*Human herpesvirus 6 (HHV-6).* Brice et al. detected HHV-6 genome in a patient with lymphomatoid papulosis in the above-mentioned study [13].

*Human herpesvirus 8 (HHV-8; Kaposi’s sarcoma—associated herpesvirus [KSHV]).* HHV-8 has been sought in vain in patients with lymphomatoid papulosis [16]. At present, there are no data on systematic attempts to detect this virus in cases of cutaneous pseudolymphomas.

Other DNA Viruses

The literature does not contain explicit information about the finding of DNA viruses in cases of cutaneous pseudolymphoma, other than in the studies mentioned above.

Virus Infection and Malignant Cutaneous Lymphoma in Humans

RNA Viruses

Human Immunodeficiency Viruses

*HIV-1.* There are a number of reports on cutaneous lymphoma associated with HIV-1 (e.g., [17–20]), but to date there have been no systematic studies on the HIV clonality in cutaneous lymphoma cells.

a) *HIV-1 infection without any apparent viral coinfection.* HIV-1-associated cutaneous lymphoma is a rare complication of HIV-1 infection. According to Esteve et al., the onset of cutaneous lymphoma in HIV infection is associated with a poor prognosis [21]. Most of the cutaneous T-cell lymphomas associated with HIV-1 are high-grade lymphomas with a fulminant course. In our study on cutaneous lymphoma in HIV-1-positive patients, we found patients with T-cell and B-cell malignancies, respectively. Histologic classification showed high-grade lymphomas in 75% of the cases. Two variants of HIV-1-associated cutaneous lymphoma...
could be described: (1) an epidermotropic T-cell subtype, clinically and morphologically resembling mycosis fungoides (MF) or Sézary syndrome (SS), which may be HTLV-I-associated [22] (see below), and (2) a nonepidermotropic subtype, which is a large-cell lymphoma associated with a poor prognosis. This mostly CD30+ variant is often positive for EBV genome (see below) and has T-cell features in some cases [23].

Crane et al. reported HIV-1-associated cases with MF-like and angioimmunoblastic lymphadenopathy with dysproteinemia (AILD)-like cutaneous T-cell lymphoma [24]. Regardless of the subtype of the cutaneous lymphoma, additional chronic hepatitis B or chronic genital herpes infections were found in some patients. A putative connection to the lymphoma has not been noted. HTLV-I status (negative western blot) was noted in some cases of MF-like T-cell lymphoma.

In 1993, Burns and Cooper stated that MF-type cutaneous T-cell lymphoma was rather unusual in association with HIV-1 and that chronic, more typical patch-plaque MF-type cutaneous T-cell lymphoma had not been seen in any HIV-1-infected individual [25]. They reported the occurrence of stage IB epidermotropic MF-type T-cell lymphoma of the skin in HIV-1-infected men with no history of AIDS. Peripheral CD4/CD8 T-lymphocyte numbers correlated neither with the predominant lesional T-cell subtype nor with the activity of the cutaneous disease. Absence of severe immunodeficiency in HIV-1-infected patients with concomitant cutaneous T-cell lymphoma may result in a slowly progressive course, since these patients’ survival is longer than that generally reported for patients with HIV-1-associated cutaneous T-cell lymphoma or peripheral T-cell malignancy.

In light of the above, a direct role of HIV-1 in the pathogenesis of cutaneous lymphoma cannot be excluded at present.

b) HIV-1 infection in association with other viral infections. According to Kierschmann et al., the large-cell subtype of HIV-1-associated cutaneous lymphoma was positive for EBV genome in 73% and for CD30+ cells in 71% of the cases examined [23] (see below). One case of anaplastic cutaneous T-cell lymphoma associated with HIV-1 infection at the stage of AIDS also revealed EBV DNA [26] (see below). It is not yet clear whether absence of EBV correlates with a better prognosis.

HTLV-I has been found in some patients with HIV-1-associated MF-like lesions [22]. Most reports on HIV-associated cutaneous lymphoma exclude HTLV-I infection solely on the basis of negative serology, despite the fact that in cases of negative serology tissue may be positive for HTLV-I genome [27]. Thus, conclusions based on serology only should be evaluated critically. Using PCR technology, Nahass et al. found no evidence of coinfection with HIV and HTLV-I in a 46-year-old man with AIDS and cutaneous T-cell lymphoma [19]. These conflicting results illustrate that HTLV-I-infection in cases of HIV-1-associated cutaneous lymphoma may constitute a secondary event.

Crane et al. reported a small number of AIDS patients with chronic genital herpes infections and cutaneous lymphomas without mentioning a possible connection between HIV, cutaneous lymphomas, and the HSV-associated genital lesions [24].

To date, an indirect role of HIV-1 in the pathogenesis of lymphomas of the skin cannot be excluded.

Human T-Cell Leukemia/Lymphoma Viruses

HTLV-I. Various diseases of the skin, ranging from infective dermatitis to cutaneous lymphoma, are thought to be associated with HTLV-I [28–32].
Although PCR technology may be a useful tool in detection of HTLV-I genome in patients with cutaneous T-cell lymphoma [e.g., 54, 55], special strategies are necessary to avoid false-positive results, which may be caused by even trace levels of contamination with viral DNA [56]. However, skin biopsies of patients with cutaneous lymphoma may also be negative for HTLV-I genome [19, 45, 56–67]. It has been suggested that positive findings of HTLV-I can differentiate cutaneous T-cell lymphoma from adult T-cell leukemia/lymphoma with skin involvement [68–70].

The involvement of HTLV in B-cell lymphomas of the skin has also been described [71]. This may be due to either secondary infection or a common HTLV-associated pathway of malignant transformation in B and T lymphocytes. However, the fact that HTLV-associated cutaneous B-cell lymphoma is an uncommon finding does not support this hypothesis.

It is unlikely that cutaneous lymphoma formation is fully dependent on the presence of HTLV-I.

b) HTLV-I infection in association with other viral infections. HTLV-I has been found concurrently with HIV-1 [22]. The literature does not support the concept that HTLV-I infection is necessary for the pathogenesis of HIV-1-associated cutaneous lymphoma.

HTLV-II. HTLV-II sequences were found in DNA extracted from peripheral blood mononuclear cells from one patient with MF [72]. An association between HTLV-II and subsets of cutaneous T-cell lymphomas has long been suspected, and the above-mentioned findings support this idea. Only few patients with lymphoma of the skin have antibodies to structural proteins or have detectable gene sequences of this retrovirus [49, 60]. A molecular search for genome of the HTLV-II gag and tax regions in skin lesions from patients with MF yielded negative results [62]. In another study, the PCR method failed to identify HTLV-II genome in biopsies of patients with cutaneous T-cell lymphoma [61]. Searching for viral agents in a patient with recurrent cutaneous anaplastic large-cell (CD30+) lymphoma, Borisch et al. detected EBV, but their search for HTLV-II was negative [58].

Thus, HTLV-II does not seem to play a major role in the pathogenesis of cutaneous lymphoproliferative disorders.

HTLV-V. In 1987 Manzari et al. described a new retrovirus and proposed the name HTLV-V [73]. The virus is related to but distinct from HTLV-I, HTLV-II, and HIV-1. It has been reported in cases of MF [74], but its role in the pathogenesis of this disease and other ailments is still obscure.

Other RNA Viruses

The literature does not provide information about the finding of RNA viruses, other than the ones listed above, in association with cutaneous lymphoma.

DNA Viruses

Herpesviruses

a) HSV-1 and HSV-2 infections without any apparent viral coinfection. Duvic et al. and Lee et al. found evidence of HSV-1 and HSV-2 in MF [75, 76]. These results were contradicted in 1993 by Brice et al., who examined biopsy specimens of cutaneous T-cell lymphoma for the presence of genome of these viruses, using the PCR method [13]. All their specimens were negative.

The literature does not provide further information about how (if at all) HSV-1 or HSV-2 contributes to the pathogenesis of cutaneous lymphomas.

b) HSV-1 and HSV-2 infections in association with other viral infections. In the above-mentioned study [24], the authors did not mention whether they had searched for a connection between chronic genital herpes infections, cutaneous lymphomas, and HIV infection. No further information on the etiologic role of HSV-1 or HSV-2 in HIV-associated cutaneous lymphoma is given in the literature.

HHV-3 (VZV). Scheman et al. had the chance to observe the course of a 68-year-old man suffering from SS along with VZV infection (herpes zoster), in whom treatment with acyclovir caused partial resolution of symptoms [77]. Although VZV infection was a secondary event, this article will be discussed in more detail below.

The literature on cutaneous lymphoma does not provide proof that VZV has a primary pathogenic role.

HHV-4 (EBV). According to Meijer et al., distribution of EBV in T-cell non-Hodgkin’s lymphoma (T-NHL) seems to be associated with the site of the malignancy; unlike in nasal, lung, and gastrointestinal T-NHL, EBV is rarely found in cutaneous T-cell lymphoma [78, 79]. It is not yet known whether this correlates with the tissue distribution of EBV subtypes [15]. Although it is an important factor, very few publications mention treatment (e.g., with methotrexate, as mentioned above [14]) prior to EBV detection experiments.

a) EBV infection without any apparent viral coinfection. Most cultures of peripheral blood mononuclear cells from patients with MF or SS yield EBV [80]. For this reason, among others, the role of EBV in the pathogenesis of cutaneous lymphoma is the subject of prolonged discussion (e.g., [81, 82]). Reactivation of EBV may perhaps be responsible for the findings in a large number of publications discussed in this article. In individual cases this virus has been suspected of having an influence on the prognosis for a patient [83]. In particular, immunohistological expression of LMP1 protein was considered to be associated with poor outcome [79]. Other authors do not believe EBV infection influences prognosis [84].

Lee et al. described 100% positivity for antibodies to EBV among their patients with cutaneous T-cell lymphoma, but these results must be viewed in light of the 60% positivity they found among healthy controls [85]. Peris et al. investigated cutaneous lymphoma patients for EBV DNA [12]. Positive findings were restricted neither to the T-cell or B-cell variant of cutaneous lymphomas nor to the respective histologic subsets. EBERs were not detected, thus suggesting a latent infection.

In 1993, Su et al. described two distinct clinicopathologic subsets of EBV-associated cutaneous lymphoma: the angiocentric T-cell lymphoma or lymphomatoid granulomatosis (type III cutaneous T-cell lymphoma) and the T large-cell lymphoma (type II cutaneous T-cell lymphoma), regardless of the Ki-1 antigen (CD30) expression [86]. These EBV-associated cutaneous T-cell lymphomas had three features in common: (1) resistance to con-
viral chemotheray, (2) poor prognosis, and (3) terminal manifestation of a hemophagocytic syndrome. This is in keeping with the findings of Tsai et al. [87] and Misago et al. [88], who reported on EBV-associated angio-centric T-cell lymphoma of the skin. This constellation may be rapidly progressive, responding poorly to aggressive conventional treatment. On the basis of one case in 1994, Harada et al. suggested a connection between EBV infection and a hemophagocytic manifestation of cutaneous lymphoma [89].

EBV is closely associated with posttransplantation lymphoma [90], seemingly with a predilection for extranodal sites. McGregor et al. suggested a possible pathogenic role of EBV in posttransplantation cutaneous B-cell lymphoma [91]. On the other hand, virus infection may also have occurred at a very early stage of tumorigenesis. This may have been facilitated by (initially local) immunodeficiency or altered clearance.

In 1997, Iwatsuki et al. conducted a retrospective survey on latent EBV in cutaneous lymphoproliferative disorder and described a variety of histologic subtypes distinct from MF or SS (e.g., angio-centric lymphoma and histiocytoid lymphoma) [92]. Su et al. also did not find EBV genome in classic MF (type I cutaneous T-cell lymphoma) [86]. This is consistent with the findings of Kerschmann et al., who described the absence of EBV genome in the epidermotropic subtype of HIV-1-associated cutaneous T-cell lymphoma, which is morphologically and clinically reminiscent of MF or SS (see above) [23].

In addition, Angel et al. [93], Brice et al. [13], Peris et al. [94], and Suzushima et al. [95] tried unsuccessfully to detect EBV genome in T-cell lymphomas of the skin or Ki-1-positive cutaneous anaplastic large-cell lymphomas. Furthermore, the cell line of a cutaneous T-cell lymphoma that Poiesz et al. were able to establish was negative for EBV nuclear antigen [36]. The role of EBV in the pathogenesis of cutaneous lymphoma is most obscure. EBV either may be the only viral agent in patients with a cutaneous lymphoproliferative disorder [58] or may be expressed in association with other viruses (as discussed below). However, the available evidence seems to indicate that EBV alone does not play a major role in the pathogenesis of cutaneous lymphoma.

b) EBV infection in association with other viral infections. Dual infection with HIV-1 was found in an AIDS-associated case of anaplastic cutaneous T-cell lymphoma (see above) [26]. More than 50% of the nonepidermotropic CD30+ large-cell-type cutaneous T-cell lymphomas investigated by Kerschmann et al. were positive for EBV genome (see above), whereas no EBV genome was found in the MF-like or SS-like epidermotropic subtype of HIV-1-associated cutaneous T-cell lymphoma [23] (see above).

Although the information may be of importance, the literature on EBV in cutaneous lymphoma does not identify the viral subtype for which the search was conducted. The subtypes of EBV (EBV-1 and EBV-2 or EBV-A and EBV-B) have been reported to differ in terms of EBV-2 nuclear antigen products, the exon C of the LMP gene, and their tissue distribution (e.g., [15]). This may account for some but not all interstudy differences. However, coinfections of EBV along with other viruses do not seem to have a major impact on lymphoma formation in the skin.

HHV-6. HHV-6 was first described as occurring in six patients, one of whom had cutaneous T-cell lymphoma [96]. Brice et al. found HHV-6 genome in both a patient with cutaneous T-cell lymphoma and a patient with lymphomatoid papulosis from the control group [13]. We have conducted numerous studies on the properties of HHV-6 (e.g., [97]) and were unable to link them with an increased rate of cutaneous lymphoma.

HHV-7. In several studies on the role of HHV-7 in various diseases (e.g., [97]) we did not find evidence of an increased rate of cutaneous lymphoma in infected individuals. This is in keeping with the body of literature on this virus: so far there are no data on the finding of HHV-7 in cutaneous lymphoma.

HHV-8. Kaposi’s sarcoma is (regardless of its etiology) associated with the presence of HHV-8. This recently discovered member of the herpesvirus family is reportedly associated with various diseases [98], including cutaneous lymphoproliferative disorders (MF) [99].

a) HHV-8 infection without any apparent viral coinfection. Some patients with cutaneous lymphoma (T-cell or B-cell variant) who are negative for HIV-1, HIV-2, HTLV-I, and/or HTLV-II may develop Kaposi’s sarcoma [100, 101]. Lymphoma-associated immunosuppression helps promote symptomatic HHV-8 infection, and the relatively low lesional virus load has been considered to be indicative of secondary infection [100]. This hypothesis is in general agreement with results of studies in which investigators were unable to identify HHV-8 in patients with cutaneous lymphoma [16, 102, 103]. So far, no HHV-8-positive, HIV-negative patients with lymphomas of the skin without Kaposi’s sarcoma have been reported.

b) HHV-8 infection in association with other viral infections. Cutaneous lymphomas have been reported to occur in patients with HIV-associated Kaposi’s sarcoma (e.g., [19, 24]). In such cases it is possible that, due to secondary infection, HHV-8 genome may be found within cutaneous lymphoma cells.

Other DNA Viruses

There is no information in the literature about identification of DNA viruses, other than the ones listed above, in cutaneous lymphoma.

Indirect Signs of a Pathogenic Role of Viruses in Pseudolymphomas and Lymphomas with Primary Cutaneous Manifestation

Antiviral drugs have been reported in association with successful treatment of cutaneous T-cell lymphoma [77, 104–106]. This may be interpreted as an indirect sign of the major role viruses might play in the pathogenesis of cutaneous malignant lymphoma. In two publications with possibly overlapping study populations, α-interferon (which is known to inhibit viral replication) was said to be one of the most effective single agents for treatment of some subsets of cutaneous T-cell lymphoma (MF and SS) [105, 106]. In two case reports, treatment with acyclovir was shown to be associated with abatement of SS lesions [77, 104]. However, as long as phosphorylation of acyclovir into a toxic anabolite can be definitely ruled out as being a property of some tumor cell clones, these data may be interpreted as strong evidence of the virus-associated development of at least some subsets of cutaneous T-cell lymphoma.
At present, there is no respective body of literature on cutaneous pseudolymphomas.

Animal Models

Reports on animals developing cutaneous lymphoproliferative disorder secondary to infection with any of the above-mentioned viruses are scarce. In some cases virus involvement has had to remain conjectural (e.g., [71]). The following section may serve as an introduction helpful for future studies on the pathogenesis of or therapy for cutaneous lymphoproliferative disorders.

Human Pathogenic Viruses Associated with Cutaneous Pseudolymphoma in Animals

RNA Viruses

HTLV-I. Rabbit cell lines are susceptible to HTLV-I [107]. Simpson et al. described an experimental scenario of a New Zealand White rabbit with chronic HTLV-I infection and cutaneous lymphoproliferative lesions [28]. Skin biopsies revealed a pattern mimicking cutaneous T-cell lymphoma, showing benign HTLV-I-positive epidermotropic T-cell infiltrates, including Sezary-like cells. The lesion could thus be considered cutaneous T-cell pseudolymphoma. The authors concluded that this lymphoproliferative skin lesion could further establish the New Zealand White rabbit (if inoculated with the cell line RH/K34) as a suitable model for studies on illnesses associated with HTLV-I. It remains doubtful if HTLV-I would ever play a major role in rabbit diseases outside a laboratory environment.

Other Viruses

The literature provides no information about the finding of cutaneous pseudolymphoma-associated human pathogenic viruses, other than HTLV-I, in animals.

Human Pathogenic Viruses Associated with Malignant Cutaneous Lymphoma in Animals

RNA Viruses

HTLV-I. Whilst the New Zealand White rabbit has been suggested as a possible animal model for HTLV-I-associated cutaneous pseudolymphoma, an animal model for HTLV-I-associated cutaneous lymphoma has not yet been identified. In 1988, Burg et al. described a female patient in whom antibodies to adult T-cell leukemia–associated antigen were found [71]. It is remarkable that her spouse and their dog (a labrador) had died of thymoma and malignant lymphoma, respectively. The virological status of the husband and the dog were not reported. It was not mentioned whether the dog had cutaneous manifestations. Systematic trials to establish which breeds of dogs, if any, are most susceptible to HTLV-I would enhance the search for an animal model of an HTLV-associated malignant lymphoproliferative disorder.

Other Viruses

The literature provides no information about the finding of cutaneous lymphoma-associated human pathogenic viruses, other than HTLV-I, in animals.

Discussion

In general, lymphotropic viruses are considered to cause lymphoproliferative disorders by direct transformation or by dysregulation (secondary transformation). The latter could be due to polyclonal or oligoclonal stimulation and initiation of proliferation.

Cutaneous Pseudolymphoma

Perhaps with the exception of HIV-1 in a few cases, none of the viruses identified to date has been proven to be a causative agent of cutaneous pseudolymphoma in humans. However, findings of virus material of HTLV-V and HIV-8 (although not very likely) may be helpful in the differential diagnosis in a minority of cases. Such findings may at least be considered unusual in cases of cutaneous pseudolymphoma and should lead to careful reassessment of the diagnosis and management plans; negative findings do not exclude malignancy.

At present, the body of knowledge with regard to animal models is insufficient for proper evaluation.

Cutaneous Lymphoma

In an evaluation of the pathogenic role of viruses in humans, four groups of cutaneous lymphoma may be identified in general.

Cutaneous lymphoma without underlying virus infection. In many publications on cutaneous lymphoproliferative disorder, the search for a virus is not the major topic but is nevertheless reported, as in an article by Fattorossi et al. [59]. This may lead to underrepresentation when results are evaluated in light of other publications, simply because when investigators review the literature, articles may not be identified as important for their discussion. Furthermore, not all negative results may be published. However, the majority of surveys involving a large number of subjects seem to demonstrate negative findings.

Cutaneous lymphoma of uncertain viral load. The ratio of seronegativity for circulating virus antigens and findings of virus genome in lesional DNA has so far not been established for cutaneous lymphoproliferative disorder. Negative titers of antiviral antibodies, along with positive findings of virus genome (with use of PCR technology), have been described with regard to cutaneous lymphoma in both humans [27] and animals [108]. Conclusions regarding virus involvement in the pathogenesis of cutaneous lymphoma that are based solely on
negative serology (mostly performed in studies of HIV-positive cases) must be evaluated critically, as mentioned above. However, the majority of studies of cutaneous lymphoma in this group seems to demonstrate negative cases.

**Virus-associated cutaneous lymphoma without underlying HIV infection.** A number of publications have reported positive findings in perhaps-overlapping study populations (e.g., [6, 7, 43, 44, 109, 110]). Most of the remaining findings of viruses in HIV-negative patients with cutaneous lymphoproliferative disorders demonstrate either latent infection or reactivation. Compared to normal lymphocytes, some altered lymphoid cells may perhaps demonstrate increased susceptibility to infection by their corresponding virus (e.g., perhaps the angiocentric T-cell lymphoma and EBV). Thus, virus-positive premalignant lesions evolving to lymphoma are not necessarily strong evidence of a key role of virus infection in the pathogenesis of cutaneous lymphoma.

At a very early stage of cutaneous lymphoproliferative disorder (with only a few cells altered), the microenvironment at the lesional site perhaps demonstrates suppressed immunity open to local virus reactivation. Findings of monoclonal or oligoclonal virus populations may be due to such facilitated infection of (pre-)malignant lymphoid cells at this very early stage of lymphoma formation. However, a description of virus clonality was found in only a minority of publications.

Positive results of a virus search may conceivably also be due to altered clearance of virus [98]. Virus infection in cutaneous lymphoproliferative disorder seems to be a subset-associated, probably secondary event, perhaps almost strictly linked to a particular patient, and may be due to an aged or locally altered immune response. In most articles, virus infection could not be shown to exert a major influence on prognosis.

The findings of Roo et al. [9] and Wolff et al. [10] are consistent with the idea that the course of a lesion, especially in an immunosuppressed individual, might depend on the locus of virus integration. To further clarify the role of viruses in both the formation of cutaneous lymphoproliferative disorder and the biological behavior of this lesion, the respective loci of integration of viruses into the host’s genome has to be analyzed subset-specifically in a large number of cases. In cases of dual infection, transactivation may take place, but it is unlikely this rare occurrence plays a pathogenic role in the majority of cases of cutaneous lymphoproliferative disorder.

**HIV-associated cutaneous lymphoma (regardless of other viruses found).** Immuno compromised patients may have an increased probability of developing cutaneous lymphoma. It is possible that HIV alone may not be able to cause lymphoma. In analogy to HHV-8 and its association with Kaposi’s sarcoma, an as-yet-unknown virus may one day be found to be linked to lymphoma formation in HIV-infected individuals. The risk of developing an additional virus infection (e.g., with EBV) is of course increased by HIV-mediated immune deficiency.

Finally, some immunocompromised patients with cutaneous lymphoma host viruses (e.g., human papillomaviruses and hepatitis B virus) that may act as a cocarcinogen in the development of secondary tumors (e.g., squamous cell carcinomas) [111, 112]. These viruses apparently do not play a role in the pathogenesis of the underlying lymphoproliferative disorder, which may belong to any of the four groups mentioned above.

In light of the above, none of the viruses we know of today (with the possible exception of HIV-1) seems to be responsible for the development of the majority of cutaneous lymphomas in humans. Owing to receptor expression of the malignant clone, a virus may act as a cell type-specific secondary habitat in a particular patient. Since virus association has been reported with regard to a number of patients with cutaneous lymphoproliferative disorders, studies on virus vector-mediated gene therapy might be performed in the future, despite its hazards. The slight association between viruses and the above-mentioned skin lesions may, however, have an impact on these trials. Evaluators of results should consider that some agents used as prodreg may lead to regression of a lymphoma.

To date there are not enough data to evaluate animal models. Further studies are needed to clarify whether the results of this review are transferable to extracutaneous (e.g., nodal) lymphomas and pseudolymphomas, and these may contribute to a better understanding of the pathogenesis of these lesions as well as have an impact on future trials of therapy, such as virus vector-based gene therapy studies.

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