

# Lichen planus remission is associated with a decrease of human herpes virus type 7 protein expression in plasmacytoid dendritic cells

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**Abstract** The cause of lichen planus is still unknown. Previously we showed human herpes virus 7 (HHV-7) DNA and proteins in lesional lichen planus skin, and significantly less in non-lesional lichen planus, psoriasis or healthy skin. Remarkably, lesional lichen planus skin was infiltrated with plasmacytoid dendritic cells. If HHV-7 is associated with lichen planus, then HHV-7 replication would reduce upon lichen planus remission. HHV-7 DNA detection was performed by nested PCR and HHV-7 protein by immunohistochemistry on lesional skin biopsies from lichen planus patients before treatment and after remission. Biopsies were obtained from lichen planus lesions before treatment ( $n = 18$  patients) and after remission ( $n = 13$ ). Before treatment 61% biopsies contained HHV-7 DNA versus 8% after remission ( $P = 0.01$ ). HHV-7-protein positive cell numbers diminished significantly after remission in both dermis and epidermis. Expression of HHV-7 was mainly detected in BDCA-2 positive plasma-

cytoid dendritic cells rather than CD-3 positive lymphocytes. HHV-7 replicates in plasmacytoid dendritic cells in lesional lichen planus skin and diminishes after remission. This study further supports our hypothesis that HHV-7 is associated with lichen planus pathogenesis.

**Keywords** Herpes virus replication · Human herpes virus 7 · Lichen planus · Plasmacytoid dendritic cells · Skin disease

## Introduction

Lichen planus is clinically characterized by flat topped polygonal, itchy erythematous papules with Wickams' striae, nail deformation, and white mucosal patches [4]. The histopathological substrate comprises a dermal band like (lichenoid) lymphocytic infiltrate directed towards the basal epidermal layer with destruction of the basal membrane and apoptosis of epidermal cells (colloid bodies). A viral cause infecting skin cells has been proposed. Hepatitis C virus was epidemiologically linked to lichen planus [14], but this finding could not be confirmed in later studies [13].

We recently described an association of human herpes virus type 7 (HHV-7) DNA and large infiltrates of plasmacytoid dendritic cells (associated with virally induced inflammatory processes) in lesional skin of lichen planus patients but not in non-lesional skin of the same patients [5]. Moreover, skin of healthy volunteers and of patients with another inflammatory skin condition like psoriasis showed significantly less HHV-7 activity. Others have described plasmacytoid dendritic cell recruitment with interferon-alpha and antiviral protein MxA production, in oral and cutaneous lichen planus lesions [16, 18]. The presence of HHV-7 in lesional skin could play a role in the

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pathogenesis of lichen planus. HHV-7 is an ubiquitous organism affecting more than 90% of the adult population worldwide, and primary infection occurs mainly during early childhood [1]. Like Epstein Barr virus reactivation is associated with Burkitt lymphoma, reactivation of HHV-7 during adulthood could be associated with lichen planus. To support this hypothesis, we quantified and compared the presence of HHV-7 DNA and protein in lesional lichen planus skin before, and after treatment-induced remission.

## Materials and methods

The hospital medical ethics review board approved this study. Before entering the study, patients gave their written informed consent to participate. Skin biopsies were collected in a follow up study from the same patient group with lichen planus as described before [5]. In short, before treatment was initiated, two 4 mm full thickness skin biopsies were obtained from lesional skin. Patients were treated with 40 mg prednisone per os daily, diminished with 5 mg every other day until a daily dose of 20 mg was reached. From that point on, the prednisone dosage was diminished with 5 mg per week. If new lichen planus lesions recurred, the previous dose was administered and diminishment halted for 3 weeks. In case prednisone treatment was contra-indicated, other treatment options like topical corticosteroids, oral acitretin (0.5 mg/kg body weight) and psoralen ultraviolet A combined photo therapy were considered, depending on the extent of lesions and underlying medical conditions.

Treatment was terminated after complete clinical remission was achieved and 2 weeks later, provided no disease activity had recurred, another two biopsies were collected from recovered lesional skin adjacent to the pretreatment biopsy sites. Both time points biopsies were taken, one biopsy was processed for routine histopathology and examined by both a pathologist and a dermatologist separately to confirm the lichen planus diagnosis or signs of ongoing inflammation. The final diagnosis was made on mutual agreement and based on typical lichen planus associated dermatopathological signs like parakeratosis, wedge shaped hypergranulosis, saw-tooth configured rete ridges, vacuolar degeneration of the basal layer, colloid bodies, a band-like dermal inflammatory infiltration and pigment incontinence [17].

The second biopsy of each time point was snap frozen in liquid nitrogen, stored at minus 80°C, and thawed later for molecular biological analysis (HHV-7 DNA). DNA isolation and the nested PCR techniques have been previously described [5, 12]. The amplified fragment (296 bp) was identified by gel electrophoresis. The lower limit of detection of the PCR is 1–5 copies of HHV-7 DNA.

We performed immunohistochemistry as described before [5, 11]. The antibodies used in this study were directed against: HHV-7, clone 5E1 and clone KR4, both resulting in a similar specific staining pattern (data not shown; Advanced Biotechnologies Inc., Columbia, MD), CD3 (pan T cell marker; clone SK7, FITC-conjugated; BD Biosciences, San Jose, CA), and BDCA-2 (plasmacytoid dendritic cell marker; clone AC144, FITC conjugated; Miltenyi Biotec, Bergisch Gladbach, Germany). In the single-staining experiments we used clone 5E1 (directed against HHV-7 tegument protein pp85), but unfortunately this clone was no longer available at the time we performed the double staining. For this reason we used in the double staining experiments clone KR4 (directed against an unknown HHV-7 epitope). In brief the following sequence of steps was applied for single staining: blocking endogenous peroxidase activity; anti-HHV-7 (clone 5E1); biotin-conjugated goat anti-mouse antibody (Dako); horseradish peroxidase-conjugated streptavidin; and for clone KR4 a TSA amplification step (Perkin Elmer) was applied. In four patients specimens obtained before and after remission were double stained for HHV-7 and CD3 or for HHV-7 and BDCA-2. In this case the following incubation steps were performed: blocking endogenous peroxidase activity; anti-HHV-7 (clone KR4); biotin-conjugated goat anti-mouse antibody (Dako); horseradish peroxidase-conjugated streptavidin; TSA amplification according to the manufacturer's protocol (Perkin Elmer); an AEC kit to visualize the peroxidase activity (Vector); blocking potential available biotin, anti-mouse immunoglobulin, and peroxidase activity; FITC-BDCA-2 or FITC-CD3 antibody; rabbit anti-FITC (Dako); peroxidase-conjugated goat anti-rabbit (Dako) for BDCA-2 and phosphatase-conjugated goat anti-rabbit (Dako) for CD3; for BDCA-2 a TSA amplification step followed by phosphatase-conjugated streptavidin; and finally an AP kit (Vector) to visualize the phosphatase activity. All single-stained sections were counterstained with Mayer's hematoxylin (Fluka). The expression of single and double stained cells was counted in each entire section at 200× magnification using a standard binocular light microscope (Olympus, Tokyo, Japan) equipped with a 0.5 × 0.5 mm ocular grid. The number of cells in the epidermis was expressed per mm and the number in the dermis per mm<sup>2</sup>.

During a follow up period of 1 year, visits were scheduled every 6 months. In case a patient experienced a relapse in between follow up visits, or after the initial 1 year follow up period, extra visits were performed at the patient's initiative for additional monitoring and treatment. Patients without a relapse on record were interviewed by telephone to exclude disease reoccurrence. The Wilcoxon rank sum test was used for statistical analysis of cell counts between samples before and after remission and the

McNemar test for binominal data;  $P \leq 0.05$  was considered significant.

## Results

Eighteen patients entered this study with a mean age of  $43.9 \pm 11.5$  years at the time of inclusion (mean age of 12 males was  $41.7 \pm 10.9$  and for 6 females  $48.4 \pm 12.3$  years). The mean disease duration was  $4.7 \pm 3.3$  months (Table 1). Lesional biopsies were taken from the lower leg in 14 cases, 3 times from the trunk and in 1 patient from the wrist. Fourteen patients were treated with oral prednisone, two patients received local corticosteroid treatment, one psoralen and ultraviolet A photo therapy and one acitretin. Three patients were lost to follow up, two patients refused biopsies after remission but their relapse data could be recorded. From the remaining 13 patients, biopsies could be collected after remission. The mean treatment duration until remission was  $136 \pm 60$  days (in the prednisone treated subgroup  $134 \pm 60$  days, in the subgroup who received other treatment modalities  $148 \pm 74$  days). In 4 out of 13 biopsies a minimal remnant inflammatory infiltrate around the basal layer was still present, in spite of clinical remission.

During follow up (with a minimum period of 30 months) 9 out of 16 patients experienced a relapse of lichen planus symptoms, 6 patients within 1 year, 3 within 4 years. All relapses occurred in patients treated with oral prednisone. In 2 patients with relapses, remnant inflammation after remission had been noticed.

In 11/18 (61%) patients lichen planus affected skin contained HHV-7 specific DNA before treatment compared to 1/13 (8%) patients after remission ( $P = 0.01$ , McNemar test). In one patient (no. 15) HHV-7 DNA was detected after remission whereas before treatment no HHV-7 DNA was found.

Immunohistochemical single staining for the presence of HHV-7 tegument protein revealed that before treatment the mean number of HHV-7 positive cells was  $58.9 \pm 33.4$  per  $\text{mm}^2$  in the dermis and  $12.7 \pm 11.7$  per  $\text{mm}^2$  in the epidermis (Fig. 1). After remission the number of positive cells had dropped to  $13.3 \pm 12.2$  and  $3.3 \pm 2.2$ , respectively ( $P < 0.05$  with the paired samples *t* test).

Immunohistochemical double staining was performed on skin specimens of four patients to investigate whether HHV-7 protein expression may be associated with T cells or plasmacytoid dendritic cells, which both represent major constituents of the inflammatory infiltrate. We found a considerable number of HHV-7/BDCA-2 double positive cells in lesional lichen planus skin before treatment but not after treatment (Fig. 2). The number of single stained BDCA2 positive cells decreased approxi-

mately twofold “before treatment” compared to “after remission” (Table 1). With HHV-7/CD3 double staining, we predominantly observed single stained HHV-7 or CD3 cells whereas only an occasional double positive cell could be found (Fig. 3).

## Discussion

Lichen planus is characterized by a band-like lymphocytic infiltrate, which seems to be involved in an attack of the basal epidermal layer. It is suggested that these T lymphocytes are directed towards infected skin cells expressing viral antigens. Molecular mimicry is a second conceivable inflammatory mechanism initiated by microbial antigens or microbial-reactive T lymphocytes that cross react with self antigens sharing homology (i.e., basal layer structures).

In our previous study we localized HHV-7 pp85 antigen containing cells in lesional lichen planus tissue around dermo-epidermal junction, coinciding with the location of the inflammatory infiltrate [5]. In addition, we detected high numbers of plasmacytoid dendritic cells (cells that are associated with the clearance of virally induced diseases) within the infiltrate. The presence of HHV-7 DNA and HHV-7 antigen did not coincide with non-lesional lichen planus skin, psoriatic skin and normal skin from healthy donors. Since HHV-7 was not found in psoriatic skin (which is also characterized by a lymphocytic infiltrate) it is unlikely that HHV-7 in lichen planus is a reflection of an innocent bystander in a dense influx of lymphocytes. Moreover, in the current study we could localize HHV-7 protein, mainly in BDCA-2 positive plasmacytoid dendritic cells and sporadic in CD3 positive lymphocytes. This is remarkable since HHV-7 has been characterized as a T-lymphotropic virus [10]. Our results suggest that plasmacytoid dendritic cells can also host HHV-7. This is conceivable since plasmacytoid dendritic cells express CD4 [15], which is the main receptor used by HHV-7 to enter target cells [21].

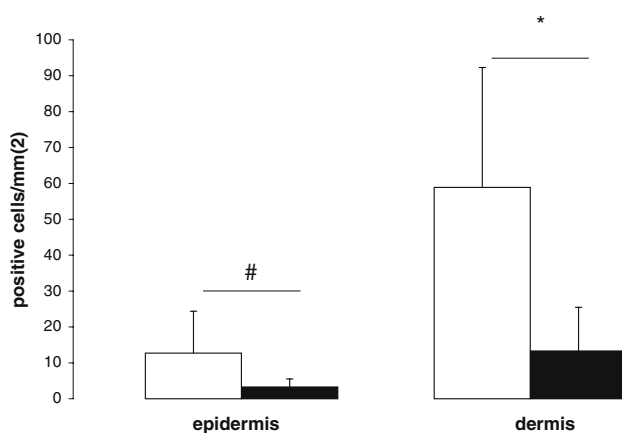
Here we investigated the effect of therapy-induced remission of lichen planus on HHV-7 replication. Both the number of HHV-7 DNA containing skin samples and the absolute number of HHV-7 antigen containing skin cells (in dermis and epidermis) diminished significantly after treatment-induced remission. Since we included a 2-week washout period between treatment termination and obtaining the post remission biopsies, a direct medication effect on viral replication is unlikely. In contrast to a fourfold diminution in HHV-7 positive cells after treatment, there was only a twofold reduction in the number of BDCA2 positive plasmacytoid dendritic cells. This makes it unlikely that the diminished HHV-7 expression only

**Table 1** Treatment characteristics and HHV-7 data before treatment and after remission

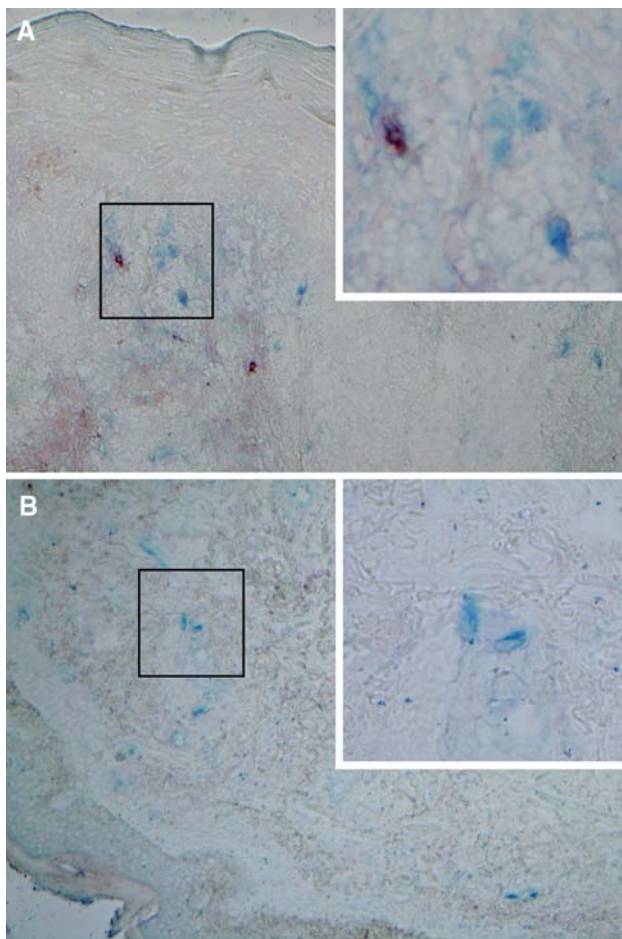
Patient	Disease duration (months)	Treatment modality	Treatment duration (days)	Biopsy site	Relapse interval (months)	Before treatment			After remission			Pathology			
						HHV-7 positive epidermal cells	HHV-7 positive dermal cells	BDCA2 double positive cells	HHV-7 positive epidermal cells	HHV-7 positive dermal cells	BDCA2 double positive cells		HHV-7 PCR		
1	12	Prednisone	66	Lower leg	5	5,1	24,7		Positive	8,8	8,8		Negative Normal		
2	2	Prednisone	169	Lower leg	13	5,7	89,2		Positive	6,2	11,1		Negative Normal		
3	12	Prednisone	139	Lower leg	None	4,7	11,7	118,7	38,7	3,3	45,3	65	11	Negative Normal	
4	5	Prednisone	72	Lower leg	1	6,7	53		Positive	NA	NA			NA NA	
5	6	Prednisone	64	Foot	6	2,4	29,4		Negative	4,7	20,5			Negative Inflamm	
6	1	Topical	NA	Foot	NA	53,8	82,9	28	13,3	Positive	NA	NA	NA	NA NA	
7	6	PUVA	96	Lower leg	None	22,3	39		Negative	2,3	5,9			Negative Inflamm	
8	1	Prednisone	75	Foot	43	16,9	67		Positive	1,8	5,3			Negative Normal	
9	4	Topical	200	Lower leg	None	9,6	23	69,7	35,3	Positive	2,9	6	38	12,3	Negative Normal
10	2	Prednisone	205	Wrist	7	16	115,9		Negative	3,2	26,9			Negative Inflamm	
11	2	Prednisone	NA	Lower leg	NA	12	34,9		Positive	NA	NA			NA NA	
12	2	Acitretin	NA	Flank	None	7,4	38,6		Positive	NA	NA			NA NA	
13	7	Prednisone	95	Back	5	13,4	66,1	187	48	Positive	4	17,7	42	6,7	Negative Normal
14	7	Prednisone	247	Lower leg	44	9	42,8		Negative	2,4	15,5			Negative Normal	
15	6	Prednisone	131	Foot	1	4,19	79,5		Negative	2	4,7			Positive Normal	
16	2	Prednisone	NA	Back	None	7,4	35,6		Negative	NA	NA			NA NA	
17	3	Prednisone	154	Foot	None	19,3	119,3		Positive	0,8	2,5			Negative Inflamm	
18	4	Prednisone	187	Foot	None	13,1	106,8	32,7	5,7	Negative	0,8	3,2	22	4,3	Negative Normal

The relapse interval was counted from discontinuation of treatment until the first relapse. HHV-7 immunohistochemical positive dermal and epidermal cells and BDCA2 positive cells were counted per mm<sup>2</sup>. Some biopsies after remission showed minimal basal layer inflammatory activity (inflamm)

NA not available



**Fig. 1** Mean cell count (in mm for the epidermis and mm<sup>2</sup> for the dermis) of HHV-7 tegument pp85 positive cells with immunohistochemical staining in lichen planus affected epidermis and dermis, before treatment (white bars) and after remission (black bars). \* and #  $P < 0.05$  with the Wilcoxon rank sum test



**Fig. 2** Double positive stained plasmacytoid dendritic cells reflects intracellular HHV-7 protein. BDCA-2 positive plasmacytoid dendritic cells (blue stain) containing HHV-7 protein (red stain) in lesional LP skin before (a) and after (b) treatment (overview 200× and inlay 400× magnification)

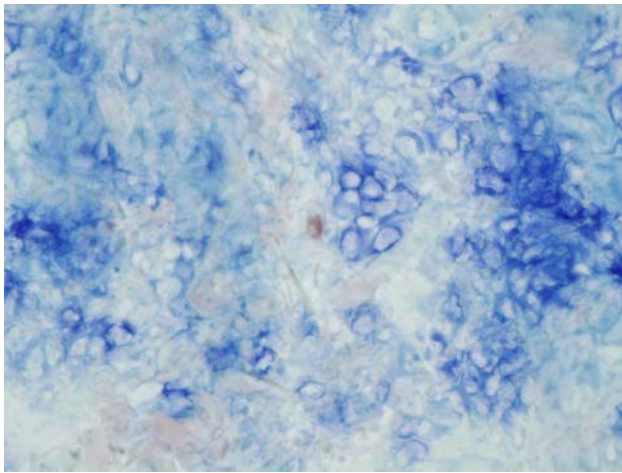
depends on a reduced number of plasmacytoid dendritic cells after treatment. Whether plasmacytoid dendritic cells are carriers of HHV-7 driving the disease activity or that these cells are infected as innocent bystanders, or actively induce the inflammatory process is not yet clear and needs further study.

HHV-7, a member of the beta herpes virus subfamily was first discovered by Frenkel et al. [10] in CD4 positive T lymphocytes of healthy individuals. It is an ubiquitous virus with a worldwide prevalence exceeding 90%. Most of the primo infections occur during infancy [1]. Since the discovery of HHV-8 as the causative agent for Kaposi sarcoma [3], all three human herpes viruses (HHV-6, -7 and -8) discovered in the last few decades have been subjected to studies on their role in skin diseases of unknown origin like pityriasis rosea [7] and exanthema subitum [2, 19].

A shared characteristic of all herpes viruses is their unique ability to persist in the host after primary infection, and become reactivated later in life (sometimes after many years of latency). Symptomatic reactivation of herpes viruses is a well-known phenomenon in the daily dermatological practice. For example, shingles afflicting patients later in life after acquisition of the causative varicella zoster virus during childhood, and the recurrence of labial and genital herpes simplex virus lesions after reactivation of viral DNA. Human herpes virus 6 reactivation is believed to cause the drug related exanthema and systemic side effect syndrome (DRESS) [6].

It is unlikely that HHV-7 primary infections cause lichen planus, since first transmission mostly occurs during childhood, whereas lichen planus affects mainly patients during midlife. Yet, it is conceivable that HHV-7 reactivation triggers lichen planus, in the same fashion as Epstein-Barr virus reactivation is associated with Burkitt lymphoma.

The apparent paradoxical efficacy of steroid therapy in lichen planus and a considered viral cause can be explained by a “hit and run” model where the actual viral reactivation would be short lived but subsequently responsible for an independently propagated inflammatory skin reaction. This could also explain why not in all patients HHV-7 was detected at the time of inclusion. Moreover, in one patient (no. 15) HHV-7 DNA was detected after remission. It is this patient that experienced a relapse 1 month later and returned to the clinic for additional treatment. Possibly HHV-7 can trigger lichen planus episodes, including relapses, but resolve before clinical lichen planus symptoms appear. The other patient (no. 4) with a relapse within 1 month unfortunately refused us a post remission skin sample. On the other hand, the absence of HHV-7 replication in some of our patients could also be explained assuming a multi causal pathogenesis for lichen planus.



**Fig. 3** HHV-7 replication does not coincide with lymphocytes. HHV-7 positive cells (red stain) and CD3 positive lymphocytes (blue stain) cells in lesional lichen planus skin are in majority mutually exclusive (400× magnification)

Further evidence for the causal association of HHV-7 and lichen planus could come from clinical studies on the efficacy of anti-herpetic medication. Which drug would be the best option is not yet clear. Guanoside analogons with little side effects like acyclovir show little activity against HHV-7 [8]. HHV-7 is more susceptible to cidofovir and foscarnet but these drugs are known for serious side effects [20].

Fredericks and Relman proposed a reconsideration of Koch's postulates for the identification of microbial antigens as causative agents in diseases [9]. With data presented here and in our previous study [5] we were able to meet with three out of their seven postulates for the establishment of a causal relationship between HHV-7 and lichen planus. (1) Microbial nucleic acid sequences were present in most cases in diseased sites and not in sites that lack pathology. (2) Fewer nucleic acid sequences were found in hosts without the disease. (3) Nucleic acid sequences correlates were present at a cellular level. The fourth postulate, a decrease of the number of nucleic acid sequences during resolution of the disease and increase with relapse, was met in this study as far as disease resolution is concerned. Unfortunately we did not collect lesional biopsies in those patients that suffered from relapses. HHV-7 reactivation during relapses will have to be investigated in future studies. (5) The number of nucleic acid sequences should correlate with disease severity and (6) reproducibility of the evidence will have to be met in future longitudinal studies. The seventh postulate, clinical features and pathology should be consistent with known biological characteristics of the microbe, will also have to be addressed in future studies since still little is known about the effects of HHV-7

in vivo yet. The hypothesis of HHV-7 as the causative agent for lichen planus deserves further research in larger studies.

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