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ORAL MEDICINE

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Current controversies in oral lichen planus: Report of an international consensus meeting. Part 1. Viral infections and etiopathogenesis

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Despite recent advances in understanding the immunopathogenesis of oral lichen planus (LP), the initial triggers of lesion formation and the essential pathogenic pathways are unknown. It is therefore not surprising that the clinical management of oral LP poses considerable difficulties to the dermatologist and the oral physician. A consensus meeting was held in France in March 2003 to discuss the most controversial aspects of oral LP. Part 1 of the meeting report focuses on (1) the relationship between oral LP and viral infection with special emphasis on hepatitis C virus (HCV), and (2) oral LP pathogenesis, in particular the immune mechanisms resulting in lymphocyte infiltration and keratinocyte apoptosis. Part 2 focuses on patient management and therapeutic approaches and includes discussion on malignant transformation of oral LP. (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;100:40-51)

Oral lichen planus (LP) is a chronic inflammatory condition that affects the oral mucous membranes with a variety of clinical presentations, including reticular,

popular, plaque-like, atrophic, and ulcerative lesions. Oral LP affects from 0.1% to about 4% of the population, it is a disease of the middle-aged, and is more common among women.¹ Although in searching for "lichen planus" more than 4000 papers could be found in the MEDLINE database by the end of 2002, many aspects of the disease are far from clear.

The authors met in France between 9 and 15 March 2003 to produce a consensus document based on the most recent literature published in peer-reviewed international journals. Some aspects of LP to be discussed were previously decided by the panel and assigned to each participant according to her or his field of expertise. During the meeting a report was presented by the author and discussed by the panel.

Selected articles published after March 2003 were included by the authors in the reference list.

The aspects of oral LP discussed and presented in the current 2-part review include viral infection and immunopathogenesis (Part 1) and clinical management and malignant potential (Part 2).²

ORAL LICHEN PLANUS AND VIRUSES

The wide range of factors that may precipitate the cell-mediated reaction resulting in oral LP lesions is

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Table I. Human papilloma virus (HPV) detection in patients affected by oral lichen planus

Country	Reference	Detection of HPV in			Specimens positive for that genotype*
		specimens of oral lichen planus (%)	Technique	HPV probe used	
Finland	Syrjanen et al 1986 ¹⁸	2/2 (100)	ISH	6,11,16	6 (1); 16 (1)
United Kingdom	Maitland et al 1987 ¹⁹	7/8 (87.5)	SBH	1,2,4,6,11,13,18	16 (6)
United States of America	Kashima et al 1990 ²⁰	0/21 (0)	ISH	6,11,16,18,31	-
Sweden	Jontell et al 1990 ²¹	6/20 (30)	SBH	6,11,16,18	11 (6)
Sweden	Jontell et al 1990 ²¹	13/20 (65)	PCR	6,11,16,18	6 (5); 11 (8); 16 (3)
United States of America	Young et al 1991 ²²	0/6 (0)	ISH	6,11,16,18,31,33,35	-
United States of America	Miller et al 1993 ²³	0/8 (0)	ISH	6,11,16,18,31,33,35,24,43,44,45,51,52,56	-
United Kingdom	Cox et al 1993 ⁵	2/4 (50)	SBH	16	16 (2)
Germany	Vesper et al 1997 ²⁴	3/7 (42)	PCR	NA	NA
Spain	Gonzalez-Moles et al 1998 ²⁵	2/17 (11.8)	PCR	16	16 (2)
Sweden	Sand et al 2000 ²⁶	6/22 (27.3)	PCR	NA	NA
Italy	Giovannelli et al 2002 ²⁷	9/34 (26.5)	PCR	NA	NA

ISH, in situ hybridization; SBH, southern blot hybridization; PCR, polymerase chain reactions; NA, not available.

*In parenthesis the number of positive specimens for that genotype.

discussed elsewhere.¹ Among the exogenous factors, several infective agents including some viruses and *Helicobacter pylori*^{3,4} have recently been linked with oral LP but sometimes on the basis of equivocal data. The present paper is focused on viral agents.

Herpes viruses

Almost all the 8 recognized human herpesviruses may give rise to oral lesions and 4 (Herpes simplex 1 [HSV-1], Epstein-Barr virus [EBV], Cytomegalovirus [CMV], Herpes virus 6 [HHV-6]) have been implicated in oral LP.

DNA from HSV-1, CMV, and HHV-6 has occasionally been found within oral LP tissue, mainly in erosive lesions and in small series.⁵⁻⁹ However, there are no significant differences in the prevalence of both immunoglobulin (Ig)G and IgM antibodies to CMV or HHV-6 between oral LP patients and controls.¹⁰ The receptor for EBV (CD21) is up-regulated in oral LP¹¹ and a significantly higher optometric density of EBV anti-earlier antigen (EA) IgG positivity has been reported in oral LP compared with controls, despite no difference in the frequency of both EBV IgG and IgM for EA and nuclear antigen-1 (EBNA).¹² Using a nested polymerase chain reaction (PCR), between 0% and 50% of oral LP samples are found to be EBV-DNA positive, but it is unclear if EBV may be involved in the pathogenesis or is secondary to the oral LP lesions.¹³⁻¹⁵

HIV

A few cases have been reported of lichenoid lesions in patients with HIV infection, but most of them could be related to zidovudine or ketoconazole therapy.^{16,17}

Human papillomavirus (HPV)

Human papillomaviruses (HPV) are small epitheliotropic DNA viruses that can induce hyperplastic, papillomatous, and verrucous squamous cell lesions in the stratified squamous epithelia. Studies to detect different HPV types in various oral mucosal diseases have been limited or have involved a small number of samples^{5,18-27} (Table I). The results appear to be equivocal, ranging from 0% to 100% of positive detection rate. It is extremely difficult to compare such results because of the many differences in inclusion criteria, clinical features (erosive vs nonerosive lesions), sampling of material (biopsies or brushing), preparation methods (fresh, frozen, or fixed), geographic differences, and methods adopted. Since highly sensitive techniques such as PCR may cause false-positive reactions,²⁸ positive results in the literature should be viewed with caution. In fact, detection of HPV-DNA does not prove a casual relationship, since its presence in the lesional tissue may be casual or result from the disease process or immunosuppressive therapy, as shown by a recent case report of HPV reactivation following treatment of penile erosive LP.²⁹

Hepatitis viruses

The frequent association of LP with chronic liver disease (CLD) is well documented, at least in Mediterranean patients with oral LP,³⁰ whereas prospective studies of Scandinavian and British oral LP patients have failed to show any significant correlation with liver diseases.³¹⁻³³ The risk of chronic liver disorders in LP patients appears to be independent of age, sex, and alcohol consumption, or a positive hepatitis B surface antigen (HBsAg) reaction.³⁴ There

Table II. Prevalence of hepatitis C virus infection in patients affected by lichen planus

Country	Reference	Study group				Control group		
		LP (n)	HCV+ (%)	Serological test	HCV-RNA (%)	Controls (n)	HCV +ve (%)	HCV RNA (%)
Brasil	Issa et al 1999 ⁴⁷	34*	5.9	Unspecified	NA	60	1.7	NA
	Figueiredo et al 2002 ⁴⁸	68**	8.8	Elisa 2	NA	***	1.4 [#]	NA
Egypt	Ibrahim et al 1999 ⁴⁹	43	20.9	Unspecified	NA	30	10 [#]	NA
France	Cribier et al 1994 ⁵⁰	52	3.8	Elisa + Riba2	NA*	112	2.6 [§]	NA
	Dupin et al 1997 ⁵¹	102**	4.9	Elisa + Riba3	NA	306	4.5 [§]	NA
Germany	Imhof et al 1997 ⁵²	83	16	Elisa + Riba2	14	87	1.1 [#]	1.1 [#]
Italy	Rebora 1994 ⁵³	56	23	Unspecified	NA	100	8	NA
	Carrozzo et al 1996 ³⁷	70**	27.1	Elisa + Riba2	21.4 [†]	70	4.3 [#]	NA
	Serpico et al 1997 ⁵⁴	100**	32	Elisa + Riba2	NA	100	3 [#]	NA
	Mignogna et al 1998 ⁵⁵	263**	28.8	Elisa + Riba2	NA	100	3 [#]	NA
Japan	Tanei et al 1995 ⁵⁶	45	37.8	Elisa 2	NA	45	6.7 [#]	NA
Nepal	Garg et al 2002 ⁵⁷	86 [‡]	0	Elisa 3	NA	43	0	NA
Nigeria	Daramola et al 2002 ⁵⁸	57	15.8	Elisa 2	NA	24	0 [#]	NA
Spain	Gimenez-Arnau et al 1995 ⁵⁹	25	44	Unspecified	NA	18	5 [#]	NA
	Sanchez-Perez et al 1996 ⁶⁰	78	20	Elisa 2	16	82	2.4 [#]	2.4 [#]
	Bagan et al 1998 ⁶¹	100**	23	Elisa + Riba2-3	NA	100	5 [#]	NA
	Glimenez-Garcia et al 2003 ⁶²	101	8.9	Elisa + Riba2	NA	99	2 [#]	NA
Turkey	Ilter et al 1998 ⁶³	72	0	Unspecified	NA	75	0 [§]	NA
	Kirtak et al 2000 ⁶⁴	73	6.8	Elisa 3	NA	73	1.4 [#]	NA
	Erkek et al 2001 ⁶⁵	54 [¶]	12.9	Elisa 3	9.3	54	3.7 [§]	NA
United Kingdom	Ingafou et al 1998 ⁶⁶	55**	0	Elisa 3	NA	110	0 [§]	NA
	Tucker et al 1999 ⁶⁷	45	0	Elisa + Riba2-3	NA	32	3 [§]	NA
United States of America	Bellman et al 1995 ⁶⁸	30	23	Elisa + Riba2	16	41	4.8 [#]	NA
	Chuang et al 1999 ⁶⁹	22	55	Elisa 2	NA	40	25 [#]	NA
	Beaird et al 2001 ⁷⁰	24	17	Unspecified	NA	20	5 [#]	NA

NA, not available.

*27% of the patients had oral lesions.

**100% had oral lesions.

***prevalence data taken from the general population of São Paulo.

†only 19 patients were tested.

‡54.3% had cutaneous lesions, 23.9% had mucutaneous lesions and 21.9% had oral lesions.

§no significant difference with the control groups.

¶38.9% had cutaneous lesions, 40.7% had mucocutaneous lesions and 20.4% had mucosal oral, genital lesions.

#significant different with the control groups.

are also few reports of mainly skin lichenoid eruptions following administration of different hepatitis B virus (HBV) vaccines.³⁵ Nevertheless, most patients with LP and CLD are not HBV-infected^{36,37} and the recently discovered viruses, hepatitis G virus and transfusion-transmitted virus, are not often associated with LP.³⁸⁻⁴¹ In addition, various hepatic conditions such as Wilson's disease, haemochromatosis, primary sclerosing cholangitis, and alpha-1-antitrypsin deficiency have rarely been related to LP,^{42,43} and the association of LP with primary biliary cirrhosis is mostly due to the administration of penicillamine treatment.^{44,45}

Hepatitis C virus

Since the first report in 1991,⁴⁶ more than 80 papers worldwide have suggested an association between LP

and hepatitis C virus (HCV) infection, among them numerous controlled studies^{37,47-70} (Table II). HCV-associated hepatic disease may precede LP onset or may be diagnosed together with it. To date, 36 studies have analyzed the prevalence of HCV infection among LP patients.⁷¹ In a recent systematic review including controlled studies, the proportion of HCV-positive subjects was higher in the LP group compared with controls in 20 of the 25 studies.⁷² The odds ratio (OR) of the pooled data from all studies was 4.80 (95% Confidence Interval [CI]: 3.25-7.09), showing a statistically significant difference in the proportion of HCV seropositive subjects among LP patients, compared with controls. When OR was calculated for oral LP patients only, it did not change substantially, whereas increased considerably in the studies from the Mediterranean

basin and halved in studies from Northern Europe, becoming not significant. However, in studies from countries with highest HCV prevalence (Egypt and Nigeria) there were negative or not significant associations,^{49,58} suggesting that any LP-HCV association cannot be explained on the basis of high prevalence in the general population only.⁷³ In addition, the few studies investigating the frequency of LP among HCV-positive subjects showed prevalences generally higher than expected (from 1.6% to 20%), independently from geographical origin.^{51,74-80} Interestingly, geographic heterogeneity in the prevalence of HCV infection was also found in patients with other HCV-related extrahepatic conditions, such as serum autoantibodies, porphyria cutanea tarda and lymphoma,⁷¹ possibly suggesting genetic differences among the populations studied. Indeed, HCV-related oral LP appears associated mainly with the HLA-DR6 allele in Italy⁸¹ and this could partially explain the peculiar geographic heterogeneity in the association between HCV and LP.

The putative pathogenetic link between LP and HCV is still under investigation but molecular mimicry between the virus and host epitopes is unlikely^{71,82,83} as well as viral factors such as genotype or viral load.⁸⁴⁻⁸⁶ The histological features of lesional tissue from HCV-positive or HCV-negative patients showed no substantial differences.^{87,88} The presence of HCV in oral LP lesional tissue has been object of several investigations^{65,89-98} (Table III). Both in situ hybridization and extractive PCR techniques revealed the presence of replicative intermediate HCV-RNA in LP specimens.^{91,93,95,96} Positive and negative strands were detected by PCR in 83% to 93% and 21% to 33% of oral LP tissue specimens, respectively.^{91,93} In addition, sequence analysis suggested a possible compartmentalization of HCV in the oral mucosa,⁹¹ although HCV may not cause direct damage to epithelial cells in oral LP lesions, since it was also found in normal mucosa.⁹⁵ Two studies failed to detect HCV antigens in either frozen or formalin-fixed sections of cutaneous LP using various immunohistochemical techniques.^{89,98}

The lympho-mononuclear infiltrate typically found in oral lichen lesions suggests that the progressive destruction of the oral mucosa lining is due to local immune aggression. A recent study showed that HCV-specific CD4+ and/or CD8+ T lymphocytes can be found in the oral mucosa of patients with chronic hepatitis C and LP.⁹² CD4+ polyclonal T-cell lines were generated more efficiently from lichen-infiltrating lympho-mononuclear cells than from peripheral blood mononuclear cells from the same patients, suggesting a higher frequency of HCV-specific T cells in the oral compartment. T-cell clones present in the oral mucosa showed a different TCR-V β chain usage than those

circulating in the peripheral blood, suggesting a specific compartmentalization at the site of the LP lesions. Furthermore, HCV-specific CD8+ T cells were present with higher frequency in mucosa tissue than in the blood and produced gamma interferon upon peptide stimulation.⁹² In view of the already mentioned demonstration of both forms of HCV-RNA in LP lesions, these results strongly suggest that HCV-specific T cells may play a role in the pathogenesis of oral LP; oral cell damage being the possible result of a direct immune aggression of epithelial cells expressing HCV antigens, possibly sustained by a cytokine environment favorable to trigger and maintain the lichenoid reactions.

IMMUNOPATHOGENESIS OF ORAL LP

A large body of evidence supports a role for immune dysregulation in the pathogenesis of oral LP, specifically involving the cellular arm of the immune system. The inflammatory infiltrate consists primarily of T cells and macrophages. Plasma cells are rarely seen and immune deposits are not characteristic.

CD8+ T cells

In oral LP, the majority of T cells within the epithelium and adjacent to damaged basal keratinocytes are activated CD8+ lymphocytes,⁹⁹⁻¹⁰³ while CD8+ T cells colocalize with apoptotic keratinocytes in oral LP lesions.^{103,104} T-cell lines and clones isolated from lichen planus lesions are more cytotoxic against autologous lesional keratinocytes than T-cell lines and clones from clinically normal skin of LP patients.¹⁰⁵ The majority of cytotoxic clones from LP lesions are CD8+ and the majority of noncytotoxic clones are CD4+. The cytotoxic activity of CD8+ lesional T-cell clones is partially inhibited by anti-MHC class I monoclonal antibody.¹⁰⁵ These data suggest that CD8+ lesional T cells may be activated, at least in part, by an antigen associated with MHC class I on basal keratinocytes and that activated CD8+ cytotoxic T cells may trigger keratinocyte apoptosis in oral LP (Fig 1). The nature of the antigen is uncertain.

CD4+ T cells

While the majority of intraepithelial lymphocytes in oral LP are CD8+, most lymphocytes in the lamina propria are CD4+.^{99,101,106} T-cell clones with helper activity and CD4+ T-cell clones that lack cytotoxic activity can be isolated from oral and cutaneous LP lesions, respectively.^{105,107} There are increased numbers of Langerhans cells (LCs) in oral LP lesions with up-regulated MHC class II expression.^{108,109} Keratinocytes in oral LP also express MHC class II antigens.^{110,111} Hence, CD4+ T cells may be activated, at least in part,

Table III. Hepatitis C virus (HCV) detection in lichen planus lesiona I tissue

Country	Reference	Detection of HCV				Oral mucosa/skin HCV RNA	
		Patients with oral lesions	Detection of HCV in specimens of lichen planus %	Technique	HCV antigens	Genomic stand n (%)	Negative strand n (%)
Italy	Sansonno et al. 1995 ⁸⁹	NA	0/7 (0)*	IP	c22, c23, c100-3	-	-
	Mangia et al. 1990 ⁹⁰	0/19	0/19 (0)	PCR	-	-	-
	Carrozzo et al. 2002 ⁹¹	12/12	10/12 (83.3)	PCR, SA, PhA	-	10 (83.3)	4 (33.3)
	Pilli et al. 2002 ⁹²	4/4	3/4 (75)	PCR	-	3 (75)	0 (0)
Japan	Nagao et al. 2000 ⁹³	14/14	13/14 (93)	PCR, SA	-	13 (93)	3 (21.4)
	Kurokawa et al. 2003 ⁹⁴	2/3	3/3 (100)	PCR	-	3 (100)	3 (100)
Spain	Arrieta et al. 2000 ⁹⁵	23/23	23/23 (100)	ISH	-	23 (100)	23 (100)
	Lazaro et al. 2002 ⁹⁶	0/5	5/5 (100)	ISH, IP	core	5 (100)	5 (100)
Turkey	Erkek et al. 2001 ⁶⁵	4/5	5/5 (100)	PCR	-	5 (100)	NA
United Kingdom	Roy et al. 2000 ⁹⁷	27/27*	0/27 (0)	PCR	-	0 (0)	NA
United State of America	Boyd et al. 1998 ⁹⁸	NA	0/25 (0)**	IP	NA	-	-

NA, not available; IP, Immunoperoxidase; PCR, polimerase chain reactions; ISH, in situ hybridization; SA, sequence analysis; PhA, phylogenetic analysis.

*All the patients were HCV seronegative.

**All but of 2 of the patients were HCV seronegative.

by antigen associated with MHC class II on LCs or keratinocytes in the developing oral LP lesion (Fig 1).

CD4+ T-cell activation and subsequent clonal expansion may underlie restricted T-cell receptor V β gene expression (especially V β 22 and V β 23) by infiltrating T cells in oral LP.¹¹² High levels of antigen expression, CD40 and CD80 coexpression and interleukin (IL)-12 secretion by MHC class II+ antigen-presenting cells (APCs) in oral LP may promote a T helper-1 (Th1) CD4+ T-cell response with IL-2 and interferon-gamma (IFN-gamma) secretion.¹¹³ In support of this, recent studies identified IFN-gamma expression by T cells adjacent to basal keratinocytes in oral LP and IFN-gamma production and secretion by oral LP lesional T cells in vitro.^{103,114,115} Furthermore, both epidermal LCs and keratinocytes are capable of producing IL-12.^{116,117}

Together, these data suggest that LCs or keratinocytes in oral LP present antigen associated with MHC class II to CD4+ helper T cells that are stimulated to secrete the Th1 cytokines IL-2 and IFN-gamma. CD8+ cytotoxic T cells may then be activated by the combination of (1) antigen associated with MHC class I on basal keratinocytes and (2) Th1 CD4+ T-cell-derived IL-2 and IFN-gamma. Activated CD8+ cytotoxic T cells then trigger basal keratinocyte apoptosis (Fig 1). Local production of IFN-gamma may maintain keratinocyte MHC class II expression, thereby contributing to oral LP chronicity.^{118,119}

Mast cells

Mast cell density is also increased in oral LP¹²⁰ and approximately 60% of mast cells are degranulated

compared with 20% in normal mucosa.¹²¹ Mast cell degranulation in oral LP releases a range of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-alpha), chymase and tryptase. In oral LP, TNF-alpha may up-regulate endothelial cell adhesion molecule (CD62E, CD54, and CD106) expression that is required for lymphocyte adhesion to the luminal surface of blood vessels and subsequent extravasation.¹²²⁻¹²⁴ In addition, clusters of mast cells and intraepithelial CD8+ T cells are seen at sites of basement membrane disruption suggesting that mast cells may play a role in epithelial basement membrane disruption in oral LP.¹²⁵ CD8+ T cells may subsequently migrate through basement membrane breaks to enter the oral LP epithelium. Matrix metalloproteinases (MMPs) are secreted as inactive proenzymes and are rapidly degraded after activation. Chymase, a mast cell protease, is a known activator of MMP-9.¹²⁶ Hence, basement membrane disruption in oral LP may be mediated by mast cell proteases directly or indirectly via activation of T-cell-secreted MMP-9.^{121,127}

Chemokines

Recent studies of cutaneous lichen planus¹²⁸ identified basal keratinocyte expression of the CC chemokine MCP-1 and two CXC chemokines MIG and IL-10. IL-8, MCP-1, and GRO gamma were expressed by IL-1-stimulated human oral keratinocytes in vitro,¹²⁹ while oral keratinocytes from oral LP patients secreted cytokines that up-regulated mononuclear cell adhesion molecule expression and transendothelial cell migration in vitro.¹³⁰ These data suggest that activated keratinocytes

secrete chemokines attracting lymphocytes and other immune cells into the developing oral LP lesion (Fig 1).^{131,132}

Various data implicate a role for T-cell–secreted regulation-upon-activation, normal T expressed and secreted (RANTES) in the pathogenesis of oral LP. T cells from oral LP express RANTES in situ.¹³³ In vitro, oral LP lesional T cells express mRNA for RANTES and TNF- α stimulation up-regulates T-cell RANTES secretion.¹²¹ Mast cells express the CCR1 RANTES receptor in oral LP in situ.¹³³ An unidentified factor in oral LP lesional T-cell supernatant, up-regulates human mast cell line (HMC-1) CCR1 mRNA expression in vitro.¹³³ Oral LP lesional T-cell supernatant stimulates HMC-1 migration in vitro, while this effect is partially blocked by anti-RANTES antibody.¹³³ The same supernatant stimulates HMC-1 degranulation in vitro with release of TNF- α and histamine. This effect is also blocked by anti-RANTES antibody.¹²¹

Hence, RANTES secreted by oral LP lesional T cells may attract mast cells into the developing oral LP lesion and subsequently stimulate mast cell degranulation. Degranulating mast cells release TNF- α , which up-regulates T-cell RANTES secretion. Such a cyclical mechanism may promote disease chronicity. Furthermore, RANTES induces expression of PI 3-kinase, which is involved in signal transduction for both chemotaxis and mitogen-activated protein kinase activation. PI 3-kinase activates Akt/protein kinase B that is an important component of the cell's prosurvival machinery.¹³⁴ Both T cells and mast cells express CCR1 in oral LP.¹³³ Hence, in addition to stimulating mast-cell chemotaxis and degranulation, RANTES secreted by lesional T cells may also prolong the survival of inflammatory cells in oral LP and thereby contribute to disease chronicity.

Antigen identity

Antigens presented by MHC class II are processed through an endosomal cellular pathway. In contrast, antigens presented by MHC class I are processed through a cytosolic cellular pathway. Hence, the putative antigen presented by MHC class II to CD4+ helper T cells in oral LP may differ from that presented by MHC class I to CD8+ cytotoxic T cells (Fig 1). Alternatively, a single antigen may gain access to both the endosomal and cytosolic cellular pathways of antigen presentation. For example, some viruses encode proteins that are available for cytosolic processing and expression in association with MHC class I. These viral proteins are also present on the plasma membrane and therefore available for endosomal processing and expression in association with MHC class II.¹³⁵ Whether 1 antigen or 2 different antigens are involved

in the pathogenesis of oral LP, it is likely that antigen presentation to both CD8+ and CD4+ T cells is required to generate CD8+ cytotoxic T-cell activity (Fig 1).

The antigen may be a self-peptide, thus defining LP as a true autoimmune disease. The role of autoimmunity in disease pathogenesis is supported by many autoimmune features of oral LP including disease chronicity, adult onset, female predilection, association with other autoimmune diseases, occasional tissue type associations, depressed immune suppressor activity in oral LP patients, and the presence of autocytotoxic T-cell clones in lichen planus lesions.^{105,136,137} Keratinocytes in oral LP show up-regulated expression of heat shock protein (HSP),¹³⁸⁻¹⁴⁰ while oral LP lesional T cells proliferate in response to HSP in vitro.¹³⁹ Keratinocyte HSP expression in oral LP may be an epiphenomenon associated with preexisting inflammation. Alternatively, keratinocyte HSP expression may be a common final pathway linking a variety of exogenous agents (systemic drugs, contact allergens, mechanical trauma, bacterial or viral infection) in disease pathogenesis. In this context, HSP expressed by oral keratinocytes may be autoantigenic. Susceptibility to oral LP may result from dysregulated HSP gene expression by stressed oral keratinocytes or from an inability to suppress an immune response following self-HSP recognition.

Antigen location

LP has a well-defined clinical distribution and there is a clear demarcation between lesional and nonlesional tissue. A possible explanation for this pattern of presentation is that keratinocytes express the LP antigen, but only at the lesion site. In other words, the clinical distribution of lichen planus is determined by the distribution of the antigen. Hence, an early event in LP lesion formation may be keratinocyte antigen expression or unmasking at the future lesion site induced by systemic drugs (lichenoid drug reaction), contact allergens in dental restorative materials or toothpastes (contact hypersensitivity reaction), mechanical trauma (Koebner phenomenon), bacterial or viral infection, or an unidentified agent. Following altered keratinocyte antigen expression, antigen-specific CD4+ and CD8+ T cells may be either (1) on routine surveillance in the epithelium and encounter the keratinocyte antigen by chance ("chance encounter" hypothesis) or (2) attracted to the epithelium by keratinocyte-derived chemokines ("directed migration" hypothesis). The "chance encounter" hypothesis is supported by findings of CD8+ T cells in normal human epidermis^{141,142} and basal cell degeneration in the absence of a dense inflammatory infiltrate in LP lesions.¹⁴³ Conversely, the "directed

Immunopathogenesis of OLP

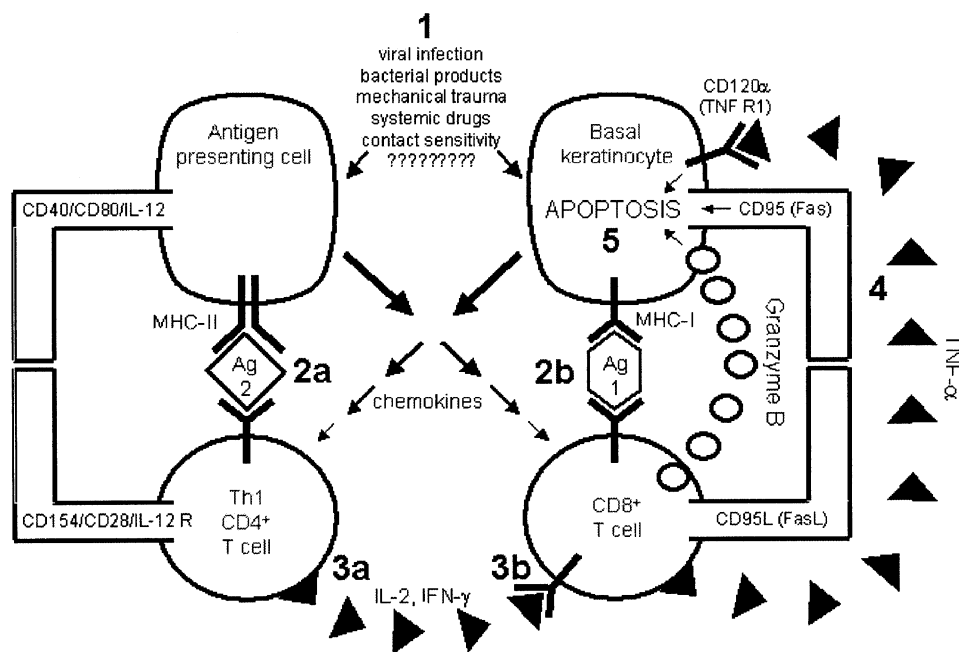


Fig 1. Hypothesis for the immunopathogenesis of oral LP. Antigen presenting cells (APCs) and basal keratinocytes are “activated” by viral infection, bacterial products, mechanical trauma, systemic drugs, contact sensitivity or an unidentified agent (1). Activated APCs and keratinocytes secrete chemokines that attract lymphocytes into the developing oral LP lesion. Activated APCs present antigen associated with MHC class II to CD4⁺ T cells (2a). Activated basal keratinocytes present antigen associated with MHC class I to CD8⁺ T cells (2b). CD40 and CD80 coexpression and IL-12 secretion by MHC class II⁺ APCs promotes a T helper-1 (Th1) CD4⁺ T-cell response. Th1 CD4⁺ helper T cells secrete IL-2 and IFN-gamma (3a), which bind their respective receptors on CD8⁺ T cells (3b). Activated antigen-specific CD8⁺ cytotoxic T cells express FasL or secrete granzyme B or TNF-alpha (4) that trigger basal keratinocyte apoptosis (5).

migration” hypothesis is supported by findings of constitutive chemokine receptor expression by naïve T cells¹⁴⁴ and a dermal T-cell infiltrate prior to the appearance of intraepithelial lymphocytes and epithelial damage in LP lesions.¹⁴⁵ In this context, keratinocyte antigen expression ± chemokine production are primary events in oral LP lesion formation, followed by keratinocyte apoptosis triggered by antigen-specific CD8⁺ cytotoxic T cells (Fig 1).

Keratinocytolysis

The mechanisms used by CD8⁺ cytotoxic T cells to trigger keratinocyte apoptosis in oral LP are unknown but possible mechanisms include (1) T-cell–secreted TNF-alpha binding TNF-alpha receptor 1 (TNF R1) on the keratinocyte surface, (2) T-cell surface CD95L (FasL) binding CD95 (Fas) on the keratinocyte surface, or (3) T-cell–secreted granzyme B entering the keratinocyte via perforin-induced membrane pores. All may activate the caspase cascade resulting in keratinocyte apoptosis (Fig 1). Serum TNF-alpha is

elevated in oral LP patients while lesional T cells contain mRNA for TNF-alpha and secrete TNF-alpha in vitro.^{103,115,146} TNF-alpha is expressed by basal keratinocytes and by T cells throughout the sub-epithelial infiltrate in oral LP. The TNF-alpha receptor TNF R1 is expressed by basal and suprabasal epithelial cells in oral LP lesions.¹⁰³ It is tempting to speculate that basal keratinocyte TNF-alpha expression in oral LP may be due to T-cell–secreted TNF-alpha binding epithelial TNF-alpha receptors. Hence, CD8⁺ cytotoxic T cells may secrete TNF-alpha that triggers keratinocyte apoptosis via TNF R1, although roles for granzyme B and Fas cannot be excluded at this stage.

ORAL LP AND GRAFT VERSUS HOST DISEASE

Graft-versus-host disease (GVHD) is a common serious complication following allogeneic hematopoietic stem cell transplantation (HSCT), and is a major cause of HSCT-related mortality.¹⁴⁷ Acute GVHD occurs within the first 100 days of transplantation and comprises dermatitis, enteritis, and

hepatitis with immunosuppression and cachexia. Chronic GVHD develops after day 100 and comprises an autoimmune-like syndrome comparable to ulcerative colitis, primary biliary cirrhosis, Sjögren's syndrome, rheumatoid arthritis, and lupus-like disease with glomerulonephritis. The skin is a primary target in chronic GVHD and exhibits either a lichenoid eruption or sclerodermatous changes.¹⁴⁸ Oral involvement occurs in 33% to 75% of patients with acute GVHD and up to 80% of patients with chronic GVHD.¹⁴⁹ Oral mucosal GVHD resembles oral LP both clinically and histologically.^{150,151} As with oral LP, squamous cell carcinoma (SCC) may develop in oral and cutaneous chronic GVHD.^{152,153}

Most patients who undergo allogeneic HSCT receive stem cells from MHC-identical donors. In these patients, GVHD is initiated by donor T cells that recognize a subset of host peptides called minor histocompatibility antigens (miHAs). Although the antigen specificity of LP and mucocutaneous GVHD is probably distinct, it is likely that they share similar immunological effector mechanisms resulting in T-cell infiltration, epithelial basement membrane disruption, basal keratinocyte apoptosis, and clinical disease. Hence, research findings in one disease may give clues to the pathophysiology of the other. The role of TNF- α as a major effector molecule in GVHD has been confirmed in a number of experimental systems. Importantly, neutralizing anti-TNF- α antibodies have been shown to alleviate cutaneous and intestinal GVHD in both mice and humans.¹⁵⁴⁻¹⁵⁷ Blockade of the CD40-CD154 costimulatory pathway prevented GVHD following allogeneic HSCT.¹⁵⁸⁻¹⁶⁰ The role of the Fas apoptotic pathway in cutaneous GVHD is less clear. In one study, the transfer of cells lacking Fas-L (CD95L) reduced the severity of murine cutaneous GVHD.¹⁶¹ In another study, recipient mice deficient in Fas (CD95) showed increased severity of cutaneous GVHD.¹⁶² An MMP inhibitor was shown recently to alleviate GVHD pathology in the liver, intestine, and hematopoietic tissues and reduce weight loss and mortality in murine GVHD.¹⁶³

To further elucidate the cellular and molecular mechanisms of lichenoid cutaneous pathology, a recent study correlated detailed histopathology with global gene expression in a murine model of cutaneous GVHD.¹⁶⁴ Cutaneous GVHD was induced by MHC-matched allogeneic HSCT, and ear skin was examined at days 7, 14, 21, and 40 posttransplantation. On day 7 post-HSCT, the skin appeared relatively normal with the only pathological changes consisting of rare dermal vessels cuffed by occasional lymphocytes and dermal mast cells containing clear cytoplasmic vacuoles indicating degranulation. By day 14, lymphocytes were

diffusely present within the dermis and focally within the epidermal layer in association with early keratinocyte apoptosis. Gene expression patterns were consistent with early infiltration and activation of CD8⁺ T and mast cells, followed by CD4⁺ T, natural killer (NK), and myeloid cells. The sequential infiltration and activation of effector cells was accompanied by up-regulated expression of many chemokines and their receptors (CXCL1, 2, 9, 10; CCL2, 5, 6, 7, 8, 9, 11, 19; CCR1, CCR5), adhesion molecules (ICAM-1, CD18, Ly69, PSGL-1, VCAM-1), molecules involved in antigen processing and presentation (TAP1 and 2, MHC class I and II, CD80), regulators of apoptosis (granzyme B, caspase 7, Bak1, Bax, and Bcl2), and interferon-inducible genes (STAT1, IRF-1, IIGP, GTPI, IGTP, Ifi202A). On day 14 and thereafter, the epidermal thickness exceeded twice that observed on day 7, and the superficial epidermis exhibited marked hypergranulosis. These observations correlated with up-regulated expression of keratins 5 and 6 (markers of keratinocyte proliferation) and small proline-rich proteins 2E and 1B (markers of keratinocyte differentiation). By days 21 and 40 post-HSCT, there were multiple foci of epidermal apoptosis and the entire dermal thickness was more than twice that observed on days 7 and 14. The latter observation was associated with up-regulated expression of IL-1 β and TGF- β 1 that stimulate fibroblast proliferation and matrix synthesis. Many acute phase proteins were up-regulated early in murine cutaneous GVHD including serum amyloid A2 (SAA2), SAA3, serpins a3g and a3n, secretory leukocyte protease inhibitor, and metallothioneins 1 and 2.¹⁶⁴ These intriguing gene expression findings in murine cutaneous GVHD are currently under investigation in oral LP.

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