STUDY

Dental Metal Allergy in Patients With Oral, Cutaneous, and Genital Lichenoid Reactions

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Background: **The subject of lichen planus (LP) and dental metal allergy long has been debated. An overwhelming majority of the existing literature focuses on mercury and gold salts in relation to oral lichen planus.**

Objective: **Our objective was to expand current knowledge regarding LP and lichenoid lesions (LL) and dental metal allergy by investigating more metals and investigating cutaneous and genital disease in addition to oral disease.**

Methods: **Fifty-one patients with known LP or LL were patch tested to a series of dental metals. Patients chose to replace their dental metals or make no revision. A telephone survey was conducted after 1 year to determine disease state.**

Results: **Thirty-eight of 51 patients (74.5%) had at least 1 positive reaction. Twenty-five of 51 patients (49.0%) showed sensitivity to at least 1 mercurial allergen. Prevalence data for patients patch tested by the North American Contact Dermatitis Group (NACDG) from 1996 to 1998 was available for chromate, cobalt, gold, nickel, and thimerosal. The prevalence of positive reactions was higher in our group than in the NACDG group for all 5 of these allergens, and statistical significance was achieved for chromate ($P = .028$), gold ($P = .041$), and thimerosal ($P = .005$). Of patients who had a positive patch test reaction to 1 or more metals, 100% (9 of 9) reported improvement after metal replacement, whereas 62.5% (15 of 24) reported improvement without metal replacement.**

Conclusion: **Sensitization to dental metals is more common among LP and LL patients than in routinely tested patients, and might be an etiologic or triggering factor in the disease.**

LICHEN PLANUS (LP) is a T cell–mediated, inflammatory, papulosquamous disease that can involve the skin, oral and genital mucosa, nails, and hair.[1-4] LP affects all races and is distributed across the world. Estimates of the prevalence of cutaneous LP in the United States range from 1% to 14%, whereas estimates for oral LP are 1% to 2%. Most patients are in their fourth to sixth decades with a predominance of female patients affected.[1,2,4] Lichenoid lesions (LL) have clinical and histopathologic similarities to LP and are included in our study.[5,6]

Oral lichenoid lesions (OLL) and oral lichen planus (OLP) are often considered idiopathic (Fig 1). Authors have used these terms interchangeably and for the purpose of this study, we considered these terms to be equivalent. Certain cases have been linked to a particular etiology such as hepatitis C, graft-versus-host disease or drug hypersensitivity or associated with diabetes mellitus, candidiasis, and lupus erythematosus.[2,5,7-9] However, it is difficult to determine if the above associations represent causal or coincidental relationships.[2]

Recent studies have shown preliminary evidence that patients with oral LP and LL and a shown allergy to dental metals improved after replacement of their dental work.[6,8-20] Those studies focused primarily on oral LP/LL and allergy to the mercury or gold salts. Our study was designed to expand current knowledge regarding LP/LL and dental metal allergy by investigating a broad spectrum of dental metals. In addition, this study is unique in that cutaneous LP/LL was studied as well.

Materials and Methods

Phase I

Potential participants were identified by searching the medical records of a tertiary dermatology center for the diagnoses of LP and LL. There was no selection criteria for age, race, or sex. Inclusion criteria were as follows (1) the subject must have a documented history of LP or LL, (2) currently have metallic dental work, such as crowns, fillings, or dentures, and (3) agree to be evaluated with patch testing.

Patch testing

Patients were patch tested by placing allergens in Finn Chambers secured with Scanpor tape (Hermal USA, Oak Hill, NY) on the upper back. The following allergens were tested: potassium dichromate 0.25% in petrolatum pet., cobalt chloride 5% pet., copper sulfate 2% pet., gold sodium thiosulfate 0.5% pet., indium (III) sulfate 10.0% in water aq., iridium (III) chloride hydrate 1.0% aq., mercury 0.5% pet., nickel sulfate hexahydrate 2.5% pet., palladium chloride 1% pet., phenylmercuric acetate 0.05% pet., silver nitrate 1% aq., and thimerosal 0.1% pet. Allergens were supplied by Chemotechnique, Malmo, Sweden. The subjects returned after 48 hours for removal of the patches and marking of the sites. The first reading was performed 15 to 30 minutes after removal of the patches to minimize the effects of pressure from the disks and dermographic erythema. Grading was performed on a scale of 0 to 3+,

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1046-199X/01/1203-0003$35.00/0

doi:10.1053/ajcd.2001.22777

based on the system used by the North American Contact Dermatitis Group (NACDG).[21] Subjects returned for a second reading from 96 hours to 7 days after application.

Phase II

Each subject who had completed Phase I of the study chose either to replace his or her dental work with another substance or make no revision in his or her dental work. All subjects, regardless of whether or not they chose to revise their dental work, were followed up by telephone survey after 1 year to assess the state of their disease as "better," "same," or "worse."

Statistical Analysis

Exact methods based on the binomial distribution were used to test for significant differences in the prevalence of positive reactions between the test group and the group tested by the NACDG.

Results

Phase I

The positive patch test results obtained for the 51 patients (34 women and 17 men) are summarized in Table 1. Patient age ranged from 17 to 82 years with a mean of 55.9 years. The duration of disease ranged from 3 months to 45 years, with a mean of 8.6 years.

Of 51 patients, 38 (74.5%) had at least 1 positive reaction. See Table 1 for detailed results. The prevalence of positive reactions was significantly higher in our test group than in the group tested by NACDG for chromate (P = .028), gold (P = .041), and thimerosal (P = .005). Of 51 patients, 25 (49.0%) showed sensitivity to 1 or more mercury containing compounds (mercury, phenylmercuric acetate, and thimerosal). The allergen that most commonly elicited a positive reaction was phenlymercuric acetate, with 14 of 51 patients (27.5%) reacting. Of the 13 positive to thimerosal, 4 reacted to one of the other mercurial allergens and 6 reacted to other metals.

Thirty-four (66.7%) of the 51 patients had OLP. Of these 34, 25 (73.5%) patients had at least 1 positive reaction. See Table 2 for detailed results. The prevalence of positive reactions to chromate and gold was significantly higher in the OLP group than in the group tested by the NACDG (P = .029 and P = 0.025, respectively). A total of 13 patients had isolated oral disease without cutaneous or genital involvement. Of these 13, 8 (61.5%) had at least 1 positive reaction. Table 3 contains individual allergen results in the isolated OLP group. The prevalence of positive reactions to chromate was significantly higher than the prevalence in the group tested by the NACDG (P = .010).

Thirteen (23.5%) of 51 had genital lichen planus (GLP) but none had genital disease alone. Ten of 13 (76.9%) patients showed 1 or more positive reactions. (See Table 2.) The prevalence of positive reactions to cobalt was significantly higher in the GLP group than in the group tested by the NACDG (P = .008).

A total of 35 subjects (68.6%) had cutaneous lichen planus (CLP). Of those with CLP, 27 of 35 (77.1%) had at least 1 positive reaction. (See Table 2.) The prevalence of positive reactions was significantly higher in the CLP group than in the group tested by the NACDG for both cobalt (P = .022) and thimerosal (P = .002).

Of the 35 patients with CLP, 13 of them had isolated cutaneous disease. Ten (76.9%) of the 13 had at least 1 positive reaction. Eleven of 13 (84.6%) were women. Patient age ranged from 17 to 81 years with a mean of 57.8 years. The duration of disease ranged from 6 months to 32 years, with a mean of 7.1 years. Table 3 contains individual

Table 1. Positive Patch Test Results for the Entire Test Group

	Positive Final Readings (n = 51)		*NACDG Percent Allergic (1996-1998)*
	Percent (No.)	*P*-Value	
Potassium dichromate 0.25% pet.	9.8% (5)	0.028*	2.8%
Cobalt chloride 5% pet.	15.7% (8)	0.169	9.0%
Copper sulfate 2% pet.	3.9% (2)		NT
Gold sodium thiosulfate 0.5% pet.	19.6% (10)	0.041*	9.5%
Indium (III) sulfate 10.0% aq.	3.9% (2)		NT
Iridium (III) chloride hydrate 1.0% aq.	3.9% (2)		NT
Mercury 0.5% pet.	7.8% (4)		NT
Nickel sulfate hexahydrate 2.5% pet.	15.7% (8)	0.896	14.2%
Palladium chloride 1% pet.	17.7% (9)		NT
Phenylmercuric acetate 0.05% pet.	27.5% (14)		NT
Silver nitrate 1% aq.	3.9% (2)		NT
Thimerosal 0.1% pet	25.5% (13)	0.005**	10.9%
One or more mercury-containing compounds (mercury, phenylmercuric acetate, and/or thimerosal)	49.0% (25)		Information not available

Abbreviations: NACDG, North American Contact Dermatitis Group; pet. in petrolatum; NT, not tested; aq.; in water.
*P < .05
**P < .01

Table 2. Positive Patch Test Results for OLP, CLP, and GLP Groups

	Final Reading (All Patients With OLP Tested) (n = 34)		*Final Reading (All Patients With CLP Tested) (n = 55)*		*Final Reading (All Patients With GLP Tested) (n = 13)*	
	Percent (No.)	*P-Value*	*Percent (No.)*	*P-Value*	*Percent (No.)*	*P-Value*
Potassium dichromate 0.25% pet.	11.8% (4)	0.029*	5.7% (2)	0.514	0% (0)	1.000
Cobalt chloride 5% pet.	11.8% (4)	0.733	22.9% (8)	0.022*	38.5% (5)	0.008**
Copper sulfate 2% pet.	2.9% (1)		5.7% (2)		7.7% (1)	
Gold sodium thiosulfate 0.5% pet.	23.5% (8)	0.025*	20.0% (7)	0.088	23.1% (3)	0.239
Indium (III) sulfate 10.0% aq.	5.9% (2)		2.9% (1)		0% (0)	
Iridium (III) chloride hydrate 1.0% aq.	5.9% (2)		2.9% (1)		7.7% (1)	
Mercury 0.5% pet.	8.8% (3)		5.7% (2)		0% (0)	
Nickel sulfate hexahydrate 2.5% pet.	11.8% (4)	0.919	20.0% (7)	0.443	7.7% (1)	0.861
Palladium chloride 1% pet.	17.7% (6)		20.0% (7)		15.4% (2)	
Phenylmercuric acetate 0.05% pet.	32.4% (11)		25.7% (9)		30.8% (4)	
Silver nitrate 1% aq.	2.9% (1)		5.7% (2)		0% (0)	
Thimerosal 0.1% pet	20.6% (7)	0.141	31.4% (11)	0.002*	15.4% (2)	0.844
One or more mercury-containing compounds (mercury, phenylmercuric acetate, and/or thimerosal)	44.1% (15)		54.3% (19)		46.2% (6)	

Abbreviations: OLP, oral lichen planus; CLP, cutaneous lichen planus; GLP, genital lichen planus; pet., in petrolatum; aq., in water.
*$P < .05$
**$P < .01$

allergen results in the isolated CLP group. Although the prevalence of positive reactions was higher in our group for 4 of the 5 allergens tested by the NACDG, none reached statistical significance at the 0.05 level.

Two patients reported flaring of their LP during patch testing. Subject number 35 was a 39-year-old man with a 10-month history of oral, cutaneous and genital LP (see Fig 2). Koebernization was observed at the sites of previous leg surgery. His history included a rash under his watch and the presence of large staples in each tibia. A previous test for hepatitis C was negative. OLP was in close proximity to dental work, but the patient denied any temporal association between LP onset and placement of new dental work. He had positive test reaction for cobalt.

The second patient who reported a flare during testing was subject number 37, a 43-year-old woman with cutaneous LP for 13 years. She had a history of jewelry allergy. She reported that LP onset had occurred soon after having several dental fillings placed. Patch testing revealed allergies to cobalt, gold, nickel, and palladium.

Of the 51 patients, 15 (29.4%) reported that onset or exacerbation of LP/LL was temporally associated with placement of dental work. Of these 15 patients, 14 of 15 (93.3%) were allergic to at least 1 of the tested allergens.

Table 3. Positive Patch Test Results for Patients With Isolated Cutaneous and Oral Disease

	Allergic Patients With Isolated Cutaneous Disease (n = 13)		*Allergic Patients With Isolated Oral Disease (n = 13)*		*NACDG Percent Allergic (1996-1998)*
	Percent (No.)	*P-Value*	*Percent (No.)*	*P-Value*	
Potassium dichromate 0.25% pet.	7.7% (1)	0.617	23.1% (3)	0.010*	2.8%
Cobalt chloride 5% pet.	23.1% (3)	0.211	0% (0)	0.587	9.0%
Copper sulfate 2% pet.	7.7% (1)		0% (0)		NT
Gold sodium thiosulfate 0.5% pet.	7.7% (1)	1.000	23.1% (3)	0.239	9.5%
Indium (III) sulfate 10.0% aq.	0% (0)		7.7% (1)		NT
Indium (III) chloride hydrate 1.0% aq.	0% (0)		7.7% (1)		NT
Mercury 0.5% pet.	7.7% (1)		15.4% (2)		NT
Nickel sulfate hexahydrate 2.5% pet.	30.8% (4)	0.202	7.7% (1)	0.861	14.2%
Palladium chloride 1% pet.	23.1% (3)		7.7% (1)		NT
Phenylmercuric acetate 0.05% pet.	15.4% (2)		23.1% (3)		NT
Silver nitrate 1% aq.	7.7% (1)		0% (0)		NT
Thimerosal 0.1% pet	30.8% (4)	0.090	15.4% (2)	0.844	10.9%
One or more mercury-containing compounds (mercury, phenylmercuric acetate, and/or thimerosal)	53.9% (7)		30.8% (4)		Information not available

Abbreviations: NACDG, North American Contact Dermatitis Group; pet., in petrolatum; aq., in water; NT, not tested.
*$p < 0.05$

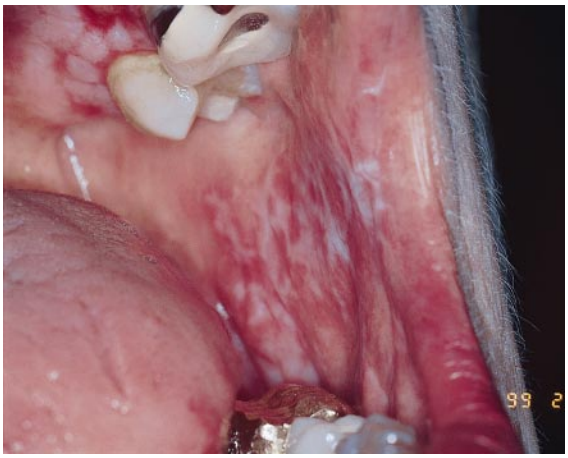

Figure 1. OLP in a patient with gold allergy.

Twenty-four of the 51 patients (47.1%) denied this temporal association. Seventeen of these 24 patients (70.8%) had a positive test reaction to at least 1 dental metal. Twelve patients could not remember if such a temporal association occurred.

Thirty-nine of 51 (76.5%) patients had active disease at the time of patch testing. Of these, 31 (79.5%) reacted to at least 1 dental metal. Of the 12 patients without active disease at the time of testing but with a documented history of LP or LL, only 7 of 12 (58.3%) had a positive reaction to at least 1 allergen.

Phase II

Of 51 subjects, 10 chose to have all or part of their dental work replaced (see Table 4). Of these 10, 9 had a positive test reaction to at least 1 metal. Nine of 9 (100%) patients with positive patch test results who chose to replace their dental metals reported an improvement on 1-year follow-up. The one patient who had a negative patch test result (100%) who chose to replace his dental metals reported improvement on 1-year follow-up.

Thirty-three of the 51 subjects did not have their dental metals replaced. Nine of the 33 had negative patch test

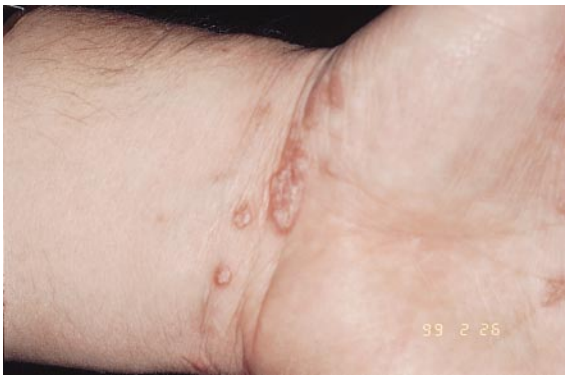

Figure 2. LP on wrist of patient with cobalt allergy.

Table 4. Phase II: Disease Assessment at 1-Year Follow-Up

	Patient's Assessment of Disease at 1-Year Follow-Up		
	Better (No.)	*Same (No.)*	*Worse (No.)*
10 subjects had metals replaced:			
Patch test positive (n = 9)	100% (9)	0	0
Patch test negative (n = 1)	100% (1)	0	0
33 subjects did not have metals replaced:			
Patch test positive (n = 24)	62.5% (15)	37.5% (9)	0
Patch test negative (n = 9)	33.3%(3)	66.6% (6)	0

NOTE. Eight subjects were unavailable for follow-up.

patch test results. Three of the 9 (33.3%) patients who had negative patch test results reported an improvement in their condition after 1 year. Of the 33 subjects, 24 who did not replace their dental metals had positive patch test results. Of the 24, 15 (62.5%) patients with positive results reported an improvement. Eight of the 51 subjects were unavailable for follow-up.

Discussion

Prevalence data for patients who underwent routine patch testing by the NACDG from 1996 to 1998 were available for the following allergens in our series: chromate, cobalt, gold, nickel, and thimerosal. The prevalence of positive reactions was higher in our test group than in the group tested by the NACDG for all 5 of these allergens, and statistical significance was achieved for chromate (P = .028), gold (P = .041), and thimerosal (P = .005) (see Table 1). The most impressive difference in prevalence between the 2 groups was for thimerosal allergy. NACDG data from 1996 to 1998 showed a 10.9% prevalence of thimerosal allergy. Our study showed a 25.5% prevalence of thimerosal allergy in patients with a documented history of LP or LL.

The origin of thimerosal allergy, has been attributed in many cases to prior inoculation with vaccines preserved with thimerosal.[22-23] The thiosalicylic acid portion of the molecule might cause reactivity in the absence of true mercury allergy, but most thimerosal allergic patients are allergic to the mercury moiety.[24] We were unable to document which of our patients received thimerosal-containing vaccines; However, there is no reason to believe our patients would be any different from the NACDG patients in this regard.

The group of 13 patients who had isolated cutaneous disease is of particular interest because to the relatively small amount of research in this area. This group provides

evidence that cutaneous LP and LL might be related to dental metal allergy. Ten (76.9%) of the 13 had at least one positive reaction. The 2 most prevalent allergens in patients with isolated cutaneous disease were nickel and thimerosal, each having a prevalence of 30.8% (4 of 13). Chromate, cobalt, nickel, and thimerosal elicited a greater percentage of positive reactions in patients with isolated CLP or CLL than in the general patch test population tested by the NACDG (see Table 3).

The 2 patients who reported a flare during patch testing might have experienced a progression of a flare that was already in progress; However, theses flares could have been initiated or exacerbated by exposure to the allergens to which the patients reacted positively. The presence of Koebnerization, as was seen in subject 35, is often noted when a patient's disease is unstable or is acutely flaring.[2]

Yiannias et al[25] recently reported a study of contact sensitivities in patients with OLP. Their study differs from the current study in that the data were collected retrospectively. Each patient was tested to standard and preservative series. Certain individuals were tested to metal, stomatitis, and/or dental series based on the physician's clinical impression of likely sensitizers. Thus, all patients in the study were not tested to the same allergens. This might account for the greater prevalence of patients with at least 1 metal sensitivity in the current study versus the Yiannias study. Thirty-eight of 51 (74.5%) of our patients and 19 of 46 (41%) of patients in the Yiannias study reacted to a metal allergen. The Yiannias study and the current study had similar numbers of participants, 46 and 51, respectively, as well as similar conclusions that contact allergy might play a significant role in patients with LP.

The greater prevalence of dental metal allergy in patients with LP and LL than in the general patch tested population suggests that an etiologic relationship exists. To more definitively determine the etiologic relationship of dental metal allergy and LP/LL, a 1-year follow-up was conducted to determine if clearing occurred on removal of dental metals. Of patients who had positive patch test reactions to at least 1 metal, 100% (9 of 9) reported improvement after metal replacement, whereas, 62.5% (15 of 24) reported improvement without metal replacement.

We realize that the data on clinical improvement are subjective and that the disease might wax and wane spontaneously. We did not attempt to assess the value of the various treatments the patients might have received because this was not an interventional study. Despite these factors, we believe the evidence clearly suggests that removal of dental metals might be beneficial in patients with chronic LP or LL.

References

1. Camisa C, Rindler, JM: Diseases of the oral mucous membranes. Curr Probl Dermatol 14:46-53, 1996
2. Boyd AS, Nelder KH: Lichen planus. J Am Acad Dermatol 25:593-619, 1991
3. Eversole LR: Immunopathogenesis of oral lichen planus and recurrent aphthous stomatitis. Semin Cutan Med Surg 16:284-294, 1997
4. Batsakis JG, Cleary KR, Cho K: Lichen planus and lichenoid lesions of the oral cavity. Ann Otol Rhinol Laryngol 103:495-497, 1994
5. Lamey P, Lewis MAO: Oral medicine in practice: Orofacial allergic reactions. Br Dent J 168:59-63, 1990
6. Lind PO, Hurlen B, Lyberg T, et al: Amalgam-related oral lichenoid reaction. Scand J Dent Res 94:448-451, 1986
7. Ostman PO, Anneroth G, Skogland A: Oral lichen planus lesions in contact with amalgam fillings: A clinical, histologic, and immunohistochemical study. Scand J Dent Res 102:172-179, 1994
8. Pang BK, Freeman S: Oral lichenoid lesions caused by allergy to mercury in amalgam fillings. Contact Dermatitis 33:423-427, 1995
9. Laeijendecker R, Van Joost T: Oral manifestations of gold allergy. J Am Acad Dermatol 30:205-209, 1994
10. Mizoguchi S, Setoyama M, Kanzaki T: Linear lichen planus in the region of the mandibular merve caused by an allergy to palladium in dental metals. Dermatology 196:268-270, 1998
11. Laine J, Kalimo K, Happonen R: Contact allergy to dental restorative materials in patients with oral lichenoid lesions. Contact Dermatitis 36:141-146, 1997
12. Sasaki G, Yokozeki H, Katayama I, et al: Three cases of linear lichen planus caused by dental metal compounds. J Dermatol 23:890-892, 1996
13. Stejskal VD, Forsbeck M, Cederbrant KE, et al: Mercury-specific lymphocytes: An indication of mercury allergy in man. J Clin Immunol 16:31-40, 1996
14. Ibbotson SH, Speight EL, Maclcod RI, et al: The relevance and effect of amalgam replacement in subjects with oral lichenoid reactions. Br J Dermatol 134:420-423, 1996
15. Alanko K, Kanerva L, Jolanki R, et al: Oral mucosal diseases investigated by patch testing with a dental screening series. Contact Dermatitis 34: 263-267, 1996
16. Koch P, Bahmer FA: Oral lichenoid lesions, mercury hypersensitivity and combined hypersensitivity to mercury and other metals: Histologically-proven reproduction of the reaction by patch testing with metal salts. Contact Dermatitis 33:323-328, 1995
17. Smart ER, Macleod RI, Lawrence CM: Resolution of lichen planus following removal of amalgam restorations in patients with proven allergy to mercury salts: A pilot study. Br Dent J 178:108-112, 1995
18. Laine J, Kalimo K, Forssell H, et al: Resolution of oral lichenoid lesions after replacement of amalgam restorations in patients allergic to mercury compounds. Br J Dermatol 126:10-15, 1992
19. Skoglund A, Egelrud T: Hypersensitivity reactions to dental materials in patients with lichenoid oral mucosal lesions and in patients with burning mouth syndrome. Scand J Dent Res 99:320-328, 1991
20. Jameson MW, Kardos TB, Kirk EEJ, et al: Mucosal reactions to amalgam restorations. J Oral Rehab 17:293-301, 1990
21. Marks JG, Belsito DV, DeLeo VA, et al: North American Contact Dermatitis Group Patch-Test Results, 1996-1998. Arch Dermatol 136:272-273, 2000
22. Moller H: All these positive tests to thimerosal. Contact Dermatitis 31:209-213, 1994
23. Osawa J, Ritamura K, Irezawa, Z, et al: A probable role for vaccines containing thimerosal in thimerosal hypersensitivity. Contact Dermatitis 24:178-182, 1991
24. Goncalo M, Figjeiredo A, Goncalo S: Hypersensitivity to thimerosal: The Sensitizing moiety. Contact Dermatitis 34:201-203, 1996
25. Yiannias JA, El-Azhary RA, Hand JH, et al: Relevant contact sensitivities in patients with the diagnosis of oral lichen planus. J Am Acad Dermatol 42:177-182, 2000