

Mucosal Lesions in an Allergy Practice

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Abstract The diagnosis and treatment of mucosal disease with an allergic pathogenesis are challenging. Oral allergy is often a hypersensitivity reaction with variable symptoms and physical exam findings. Clinical diagnosis requires a history of prior allergen exposure, a delay from exposure to clinical findings, and improvement following allergen removal. The past decades have seen great contributions to the field of oral allergy. The aim of this review is to provide an approach to the diagnosis and treatment of oral dermatologic disease with a focus on diseases with an investigated allergic pathogenesis.

Keywords Allergy · Oral · Mucosa · Diagnosis · Treatment · Patch testing

Introduction

The practicing allergist should be comfortable with the presentation of disease in the oral cavity, as this location is an

interface between the environment and host immunity. The diagnosis and treatment of oral dermatologic lesions are challenging. A wide variety of disease processes has oral manifestations, and many disease processes present with similar-appearing lesions. The aim of this review is to provide an approach to the diagnosis and treatment of oral dermatologic disease with a focus on diseases with an investigated allergic and immunologic pathogenesis.

When contrasted to the skin, the oral cavity has a natural resistance to irritants and allergens through factors that mitigate substrate interaction with the mucosa including saliva and high vascularity. The oral cavity also has a lower concentration of T lymphocytes relative to the skin, blunting an inflammatory response [1]. Allergic mechanisms are similar between skin and oral mucosa. Briefly, there are four types of allergic responses. Almost exclusively, type IV delayed reactions are responsible for oral hypersensitivity reactions but type I hypersensitivity reactions are occasionally implicated. Type I reactions are immediate. An antigen reacts with IgE tethered to mast cells leading to the release of histamine and other inflammatory mediators leading to local inflammation. Type IV hypersensitivity involves cellular immunity or delayed hypersensitivity through T lymphocytes. In type IV hypersensitivity, patients must first have prior contact and sensitization to an allergen. The sensitization phase involves allergen penetration through the mucosa and is processed and presented to CD4 helper T lymphocytes. The elicitation phase involves re-exposure to the original antigen, and memory T lymphocytes secrete cytokines that induce expression of adhesion molecules on endothelial cells which allow inflammatory cell extravasation and inflammation. Days may lapse from antigen re-exposure until mucocutaneous findings appear.

Allergic contact allergy of the mouth is a rare type IV delayed hypersensitivity. It is often difficult to distinguish from irritant stomatitis, vitamin deficiency, and nicotine

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stomatitis. Subjectively, the disorder presents with soreness and burning and occasionally loss of taste or paresthesia [2]. Clinically, its presentation is highly variable, with features ranging from perioral dermatitis, erythema, ulceration, lichenoid changes, gingivitis, and cheilitis to intraoral burning and orofacial granulomatosis. Diagnosis of oral allergy requires a history of prior exposure to the allergen, a delay from exposure to clinical signs and symptoms, and improvement following removal of the allergen. Patch testing with suspected allergens can confirm allergen sensitization. Recent literature demonstrates that in patients with any type of oral pathology, between 40 and 70 % have positive patch testing [3–5]. The most commonly reported allergens are metallic dental materials including amalgams and food flavorings and preservatives (Table 1, A).

We review an approach to evaluating oral dermatologic disease (Fig. 1). The first decision point is whether the patient is suffering primarily from an ulcerative or non-ulcerative inflammatory condition. Ulcers are small open sores with loss of the epithelium. Oral inflammation on the other hand has a highly variable presentation but typically involves local swelling and erythema. Oral ulcerative diseases with an allergic and immunologic basis are discussed in “[Section 1: Ulcerative Disorders of the Mouth with Allergic Pathogenesis](#)” while inflammatory disorders of the mouth with an allergic pathogenesis will be further explored in “[Section 2: Inflammatory Disorders of the Mouth with Allergic Pathogenesis](#)”.

Section 1: Ulcerative Disorders of the Mouth with Allergic Pathogenesis

Acute Ulcers

An acute ulcerative condition of the mouth is present for less than 6 weeks. The differential diagnosis of acute oral ulcers is broad, including traumatic causes, bacterial or viral infections, recurrent aphthous stomatitis, drug reaction, cyclic neutropenia, and occasionally allergic disease. Single episodes of ulceration are typically secondary to traumatic or infectious etiologies or are idiopathic. Recurrent ulcers can be differentiated into diseases with systemic symptoms versus recurrent aphthosis without systemic symptoms. A potential allergic pathogenesis has been recently investigated for recurrent aphthous stomatitis (RAS) and Behçet’s disease (BD).

Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis (RAS) is one of the most common oral disorders, present in all ages with a high prevalence, 17.7 %, in the general population [35, 36]. Patients usually present in their second and third decade. RAS is painful, occasionally interfering with mastication. Small erythematous papules form on

non-keratinized mucosal surfaces and progress within hours to annular ulcerations with peripheral halo-like hyperemia. Lesions are typically self-limited, resolving in weeks. However, RAS is highly recurrent. Recurrence is associated with trauma and may be provoked by foods such as citrus and spice. Hormonal fluctuations and allergic reactions have also been reported to flare the disease. Diagnosis is made by documentation of a recurrent disease course and absence of other systemic symptoms. No cure is available to date. Treatment consists of dietary elimination and topical corticosteroids for ulcer management. Topical medications such as lidocaine and oral anesthetics can reduce pain and improve quality of life.

While the etiology of RAS remains largely elusive, allergy is potentially a component. The recent literature demonstrates 15 to 50 % of patients with RAS have positive patch testing, but only 20 % of these positives are clinically relevant (Table 1, B). The most common allergen associated with RAS patch testing is vanillin, the vanilla bean component [5, 8, 9].

Further support of the allergic basis of RAS comes from allergen avoidance studies. Two double-blind trials have investigated removal of two substances, sodium lauryl sulfate and orthodontic appliances. Removal of sodium lauryl sulfate, a frequent toothpaste ingredient, was shown to significantly decrease the duration of ulcers and mean pain score in patch test-positive RAS patients [7]. Orthodontic appliance removal in RAS patients was also shown to improve RAS disease for a majority of patients [8]. However, disease improvement may be secondary to trauma reduction rather than allergen removal. RAS has been linked to food allergy, and several small studies have shown clinical response from elimination diets [10, 11, 37]. Elimination diets are not routinely recommended in RAS management as the etiology is complex and are seldom helpful in the authors’ experience.

The immunologic basis of the disease has also been investigated more frequently in recent years. Histologic studies have provided evidence for a type IV hypersensitivity reaction. In the proposed mechanism, intracellular adhesion molecules, in particular ICAM-1, enable the migration of T4 lymphocytes and neutrophils to an inflammatory site followed by epithelial invasion [38, 39]. However, other mechanisms may also be contributory. RAS patients have increased levels of T lymphocytes in the mucosa which may play a role in antibody-dependent cell-mediated response [39]. Recently, RAS patients have also been shown to have elevated salivary immunoglobulin A during acute and remission phases [40]. Additionally, evidence exists for increased mucosal levels of cytokines, including interleukin-2, CD8 T lymphocytes, and memory T lymphocytes in RAS patients [36, 41].

Behçet’s Disease

Behçet’s disease (BD) is a systemic disease with visual, digestive, nervous, and mucocutaneous manifestations. The disease

Table 1 Recent and major studies of allergic basis of oral disease

Study	Total sample size	Outcome measure
A. Oral pathology in general		
Kim et al. [3]	44	31 of 44 (70.5 %) had positive reactions; most common allergens: gold sodium thiosulfate (25.0 %) and nickel sulfate (25.0 %)
Raap et al. [6]	206	28 of 206 (13.6 %) had positive patch test to dentistry metals
Torgerson et al. [5]	331	141 of 331 (42.6 %) with positive patch test; 221 of 341 (64.8 %) total patch tests were clinically relevant; most common allergens: potassium dicyanoaurate (19.6 %), nickel sulfate hexahydrate (12.5 %), gold sodium thiosulfate (11.6 %)
Khamaysi et al. [4]	121	49 of 121 (40.5 %) had positive patch test
B. Recurrent aphthous stomatitis (RAS)		
Shim et al. [7]	90	Double-blind crossover trial with sodium lauryl sulfate toothpaste: sodium lauryl sulfate resulted in significant decrease in duration of ulcers and mean pain score but number of ulcers or disease episodes
Torgerson et al. [5]	54	14 of 54 (25.9 %) with positive patch test; 11 of 54 (20.4 %) with clinically relevant reaction; most common allergen: vanillin (33.3 %)
Pacor et al. [8]	380	Double-blind placebo-controlled trial with nickel salts: 70 of 380 (18.4 %) had positive patch test. Following orthodontic appliance removal in 70 patients, at 6 month follow-up, 28 of 70 (40.0 %) patients had complete improvement, 31 of 70 (43.7 %) partially improved, and 11 of 70 (15.7 %) were unchanged
Nolan et al. [9]	21	12 of 21 (57.1 %) had positive patch test
Wright et al. [10]	11	6 of 11 (54.5 %) responded to a dietary withdrawal dramatically within a week
Hay et al. [11]	5	4 of 5 (80 %) had improved disease with elimination diet
C. Bechet's disease (BD)		
Demirsoy et al. [12]	50	7 of 50 (14.0 %) with positive patch test; 12 of 50 (24.0 %) of control patients with positive patch test; no statistically significant difference between patients and controls
Togashi et al. [13]	10	9 of 10 (90 %) had positive skin prick test with self-saliva
D. Oral lichen planus (OLP) and oral lichenoid lesions (OLL)		
Suter et al. [14]	115	78 of 115 (67.8 %) had positive patch test to a dental material; 21 of 26 (80.8 %) with positive patch test and dental amalgam replacement had complete disease resolution; no correlation found between pathology and skin patch testing results ($P = 0.44$)
Kim et al. [3]	24	18 of 24 (75 %) with OLP had positive patch testing to dental materials; 8 of 24 (33.3 %) had positive patch test to gold sodium thiosulfate
Muris et al. [15]	906	220 of 906 (24.3 %) had positive patch test to palladium; 228 of 906 (25.2 %) had positive patch test to nickel; significant association between OLL (OR 4.7)
Ahlgren et al. [16]	83	OLL patients had significantly higher mercury and carvone positive patch tests than controls
Nishizawa et al. [17]	115	Nail lichen planus patients (10 of 15; 66.7 %) had significantly more common metal positive patch tests than OLP patients (16 of 59; 27.1 %) ($P < 0.05$); 3 of 16 (18.8 %) with OLP, positive patch test to metals and dental amalgam replacement had disease improvement; 6 of 10 (60.0 %) with nail lichen planus, positive patch test to metals and dental amalgam replacement had disease improvement
Ahlgren et al. [18]	96	27 of 96 (28.1 %) with OLL had positive patch test to gold
Gunatheesan et al. [19]	19	14 of 19 (73.7 %) with positive patch test to spearmint had co-existing OLP
Montebugnoli et al. [20]	64	14 of 64 (21.9 %) with OLL had complete clinical improvement after dental amalgam removal; 7 of 14 (50.0 %) with OLL and clinical improvement after dental amalgam removal had complete histologic healing
Torgerson et al. [5]	59	33 of 59 (55.9 %) with positive patch test; 20 of 59 (33.9 %) with clinically relevant reaction; most common allergen: potassium dicyanoaurate (28.0 %), fragrance mix (17.1 %), gold sodium thiosulfate (15.1 %), nickel sulfate hexahydrate (13.8 %), balsam of Peru (11.9 %)
Laeijendecker et al. [21]	23	11 of 13 (84.6 %) with OLP contacting dental amalgam had disease improvement following amalgam removal; 8 of 8 (100 %) with OLP 1 cm beyond dental amalgam had disease improvement following amalgam removal; 1 of 2 (50 %) with OLP 2 cm beyond dental amalgam had disease improvement following amalgam removal

Table 1 (continued)

Study	Total sample size	Outcome measure
		with OLP in no relation to dental amalgam had disease improvement following amalgam removal
Issa et al. [22]		Systematic review of 14 cohort and 5 case-controlled trials of OLL patients: 16 to 91 % with positive patch test for mercury compound; complete healing ranged from 37.5 to 100 % following dental amalgam replacement
Dunsche et al. [23]	134	37 of the 134 patients (27.6 %) with OLL had positive patch test mercury or amalgam filling; 102 of 105 (97.1 %) with OLP and dental amalgam removal had disease improvement regardless of patch test results
Wong et al. [24]	84	33 of 84 (39.3 %) with OLL had positive patch test; 28 of 30 (93.3 %) with OLP and amalgam replacement had symptom improvement in 3 months
Scalf et al. [25]	51	38 of 51 (74.5 %) with OLL had positive patch test; 25 of 51 (49.0 %) had positive patch test to mercury; 9 of 9 with OLL, positive metal patch test and amalgam replacement had disease improvement; 15 of 24 (62.5 %) with OLL had disease improvement without amalgam replacement
E. Orofacial granulomatosis		
Fitzpatrick et al. [26]	120	8 of 120 (6.7 %) had positive patch test with benzoate and cinnamon; 66 of 120 (55.0 %) had positive urticarial testing with benzoate and cinnamon
Campbell et al. [27]		Comprehensive literature search: Most common allergens by patch test were benzoic acid (36 %), food additives (33 %), perfumes and flavorings (28 %), cinnamaldehyde (27 %), cinnamon (17 %), benzoates (17 %), and chocolate (11 %); 54–78 % of OFG benefit from cinnamon- and benzoate-free diet
Torgerson et al. [5]	13	4 of 13 (30.1 %) with positive patch test; 0 of 13 (0 %) with clinically relevant reaction; most common allergens: nickel sulfate hexahydrate (15.4 %), benzoyl peroxide (7.7 %), dodecyl gallate (7.7 %), gold sodium thiosulfate (7.7 %)
White et al. [28]	25	18 of 25 (72.0 %) of OFG on cinnamon- and benzoate-free diet for 8 weeks had clinical response
Patton et al. [29]	80	14 of 80 (17.5 %) with OFG had intolerance to cinnamaldehyde, carvone and piperitone
F. Allergic contact cheilitis		
O’Gorman and Torgerson [30]	41	Most common allergens: fragrance mix (11 of 41; 26.8 %), <i>Myroxylon pereirae</i> resin (10 of 41; 24.4 %), dodecyl gallate (9 of 41; 22.0 %), octyl gallate (6 of 41; 14.6 %), and benzoic acid (5 of 40; 12.5 %). Nickel (8 of 40; 20.0 %) was the most relevant metal allergen
Schena et al. [31]	129	110 of 129 (85.3 %) with positive patch test; 84 of 129 (65.1 %) clinically relevant patch testing reaction; most common allergens: nickel, fragrances, balsam of Peru, chromium salts and manganese salts, dental materials, oral hygiene products; 21 of 129 (16.3 %) cases of cheilitis were diagnosed irritant contact cheilitis
Torgerson et al. [5]	54	14 of 54 (26.9 %) with positive patch test; 11 of 54 (20.4 %) with clinically relevant reaction; most common allergen: fragrance mix (13.0 %), gold sodium thiosulfate (6.8 %), dodecyl gallate (6.1 %), caine mix III (5.6 %), benzoic acid (4.0 %)
Lim and Goh [32]	81	Most common allergens: lip cosmetics in 44 of 81 (54 %), toothpaste 17 of 81 (21 %), topical medications in 6 of 81 (7 %)
G. Secondary burning mouth syndrome		
Torgerson et al. [5]	145	61 of 145 (42.1 %) with positive patch test; 35 of 145 (24.1 %) with clinically relevant reaction; most common allergens: potassium dicyanoaurate (16.4 %), nickel sulfate hexahydrate (12.3 %), gold sodium thiosulfate (10.9 %), palladium chloride (9.3 %), fragrance mix (8.3 %)
Steele et al. [33]	75	28 of 75 (37.3 %) with positive patch test; most common allergens: nickel sulfate hexahydrate (28.6 %), balsam of Peru (28.6 %), gold sodium thiosulfate (28.6 %)
H. Plasma cell gingivitis—atypical gingivitis		
Silverman and Lozada [34]	16	11 of 16 (69 %) with plasma cell gingivitis were gum chewers; 2 of 16 (12.5 %) who avoided gum chewing had disease resolution without recurrence

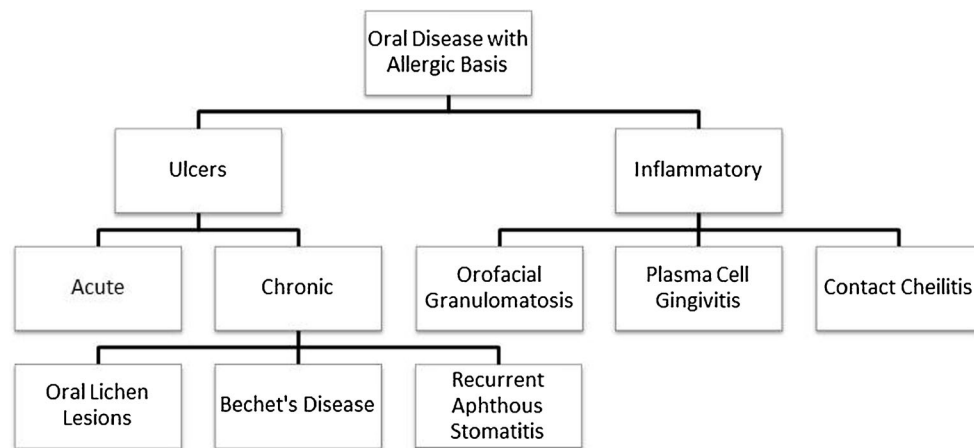


Fig. 1 Diagnostic algorithm for oral disease with an allergic basis. First decision point is ulcerative versus non-ulcerative oral disease. Acute ulcerative oral disease is less than 6 weeks of ulcer duration. The differential diagnosis of acute oral ulcers is broad including traumatic causes, bacterial or viral infection, recurrent aphthous stomatitis, drug reaction, cyclic neutropenia, and occasionally allergic disease. The

differential for chronic oral ulcers present for more than 6 weeks includes oral lichen, Bechet's disease and recurrent aphthous stomatitis. The main non-ulcerative, inflammatory disorders of the mouth with an investigated allergic pathogenesis are orofacial granulomatosis, plasma cell gingivitis, and contact cheilitis

is rare in North Americans, but more frequent in Mediterranean and Asian patients. BD diagnosis involves documentation of recurrent aphthous ulceration with several recurrences and the presence of two other classic features including genital ulceration, positive pathergy test, ocular manifestations, or cutaneous lesions including erythema nodosum or acneiform nodules in post-adolescent patients. Oral ulceration is most often the initial sign of BD. On oral exam, painful ulcers are found on the tongue, lips, gingivae, buccal mucosae, and nasal cavity. Lesions are sharply demarcated with a gray base and a surrounding red halo. Genital ulcerations resemble the oral lesions but are usually larger in size. Ulcerations persist for approximately 1 to 2 weeks before resolution [42]. A fetid oral odor may also be observed. By history, patients describe photophobia, periorbital pain, and neurologic findings resembling multiple sclerosis with frequent symptom remission and exacerbation.

Unfortunately, lifelong disease recurrence can be expected in BD. Several systemic treatment options for prevention of oral ulcer recurrence include colchicine, dapsone, thalidomide, and methotrexate. However, no treatment option has been proven to be superior.

To date, investigations into the pathogenesis of BD have identified a wide array of potential causes. However, the primary manifestation of BD is a small, medium, and large vessel vasculitis. Histologic studies have demonstrated a perivascular, leukocytoclastic, obliterative vasculitis of arteries, veins, and capillaries [43]. Among the other potential etiological drivers of BD are genetics, epigenetics, the innate immune system, and bacterial cross-reactivity. Prior studies have shown a potential genetic basis for BD linked to HLA-B51 [44]. Evidence also exists for an epigenetic BD mechanism involving alterations in DNA methylation [45].

Laboratory studies have demonstrated a potential role of the innate immune system via defects in toll-like receptors and increased in vitro neutrophil motility [46, 47]. Finally, bacterial cross-reactivity with streptococcal, parvovirus B19 and *Helicobacter pylori* antigens has been linked to BD in some investigative reports [48, 49].

Evidence for allergic pathogenesis in BD is limited. A small study showed the majority of BD patients had positive skin prick test with self-saliva. In a larger study, positive patch testing in BD patients demonstrated no significant difference when compared to controls, arguing against an allergic component of the disease (Table 1, C). Immunologically, there is evidence for an innate immune mechanism of disease involving hypersensitivity reaction to oral streptococci. Patients have been shown to have delayed-type cutaneous hypersensitivity reactions with skin testing of streptococcal antigens [50]. Also, a study of 11 patients showed excessive CD4 T cells producing IL-17 and IFN- γ [51].

Chronic Ulcers

Oral Lichen Planus and Oral Lichenoid Lesions

The onset of oral lichen planus (OLP) is typically the 4th or 5th decade, and women present earlier and more often than their male counterparts. OLP can present as a chronic, superficial ulcerative disease of the mouth in its ulcerative or erosive subtype. There are two other key subtypes of OLP including the reticular subtype, featuring a white, lacy appearance on the buccal mucosa, and the atrophic subtype, with painful, burning red plaques. Patients may exhibit more than one subtype at the same time. Oral ulcers localize to any portion of the oral mucosa. The buccal mucosa, gingivae, and tongue are the

most common locations. The presentation of OLP in association with dental amalgam is a white, thickened lesion known as lichenoid contact stomatitis usually adjacent to the offending dental material.

Diagnosis of OLP is clinical with confirmatory biopsy. Approximately one in ten patients with OLP will also have skin lesions. Vulvar and vaginal lichen planus also features erythema and erosion. Patients complain of pain and a burning sensation. Similar to vulvovaginal lichen planus, OLP has a chronic course with rare remission. It should be noted that OLP increases the risk of both cutaneous lichen planus as well as oral malignancy. Treatment involves high-potency topical corticosteroids with corticosteroid injections for refractory disease [52].

Ulcerative or erosive disease can be managed with topical tacrolimus, which has been validated by placebo-controlled trials [53, 54]. Topical isotretinoin can also be effective; however, retinoids are not well tolerated by many patients. Systemic treatment may be required for severe disease.

The etiology of OLP is uncertain but is believed to involve allergy, trauma, medication reactions, and autoimmune activation of lymphocytes against basal cell layer keratinocytes.

OLP is considered a CD8 T lymphocyte-mediated assault on basal epithelial cells. Keratinocytes activate CD8 T lymphocytes. T lymphocytes further inflammation through chemokine release and cause widespread keratinocyte apoptosis through direct ligand interaction or indirect cell signaling [55]. Additionally, evidence for a genetic predisposition to OLP has been found through the genetic analysis of the cell signaling proteins and cytokines of OLP patients [56, 57].

There is a relative abundance of patch testing literature (Table 1, D). In terms of general dental materials, positive patch testing results in OLP patients vary from 60 to 80 % [3, 14]. Mercury is highly allergenic and often present in dental amalgams. A systematic review of 14 cohort and five case-controlled trials of patients with oral lichenoid lesion (OLL) demonstrated that a wide number of oral lichenoid lesion patients have positive patch tests for mercury-containing compounds [22]. Another controlled study demonstrated contact allergy to mercury was statistically higher in the OLP than in controls [16]. However, allergen reaction to mercury is not limited to OLP. Cutaneous and genital lichenoid reactions also feature positive patch test reactions [25, 58].

The association between OLP and other metals has been investigated. Positive patch testing to gold sodium thiosulfate has been noted in a subset of OLP patients [3, 18]. A large study found positive patch testing to nickel and palladium metals in approximately a quarter of OLP patients [15]. Of note, a recent study demonstrated the prevalence of positive reactions to metals in OLP patients was significantly less likely than in nail lichen planus patients [17]. Other allergens that have been linked to OLP include the oil terpenoid carvone, potassium dicyanoaurate, and balsam of Peru [5, 16].

There is a body of research on the clinical results of OLP patients following dental amalgam removal and its association with patch testing [14, 17, 20–25]. A systematic review of 14 cohort and five case-controlled trials of patients with OLP demonstrated that after dental amalgam replacement, between 35 and 100 % of patients had complete disease resolution. Disease improvement occurred most frequently in lesions located adjacent to the dental amalgam [22]. Another study showed around half of OLP patients that experienced clinical improvement after dental amalgam removal had corresponding resolution of OLP histologic findings [20].

The literature is conflicted on the predictive benefit of patch testing in OLP patients prior to amalgam removal. A review by Rogers et al. suggests preoperative patch testing in OLP patients in order to identify patients with mercury allergy that are more likely to improve following amalgam removal [58]. However, the findings of a large investigation suggest patch testing results are not indicative of clinical benefit from amalgam removal, as 102 of 105 (97.1 %) patients with OLP and dental amalgam removal had disease improvement regardless of their patch testing results [23].

Patients with oral lichenoid disease in proximity to dental amalgams are entitled to a discussion of the risks and benefits of amalgam removal. Though invasive, the likelihood of disease resolution makes amalgam removal an attractive option. Factors such as disease severity, response to topical steroid therapy, disease proximity to amalgam fillings, and the potential cost of operation must be considered when advising treatment approach.

Section 2: Inflammatory Disorders of the Mouth with Allergic Pathogenesis

The main non-ulcerative, inflammatory disorders of the mouth with an investigated allergic pathogenesis are orofacial granulomatosis, plasma cell gingivitis, and contact cheilitis.

Orofacial Granulomatosis

The classic presentation of orofacial granulomatosis (OFG) is a non-tender, recurrent lip swelling persisting for weeks to months. On examination during active disease, lip protrusion will be observed. Other findings may include mid-lip fissuring, angular cheilitis, and tongue fissuring. A facial palsy and cervical lymphadenopathy can also be observed as noted in Melkersson-Rosenthal syndrome with paralysis of the facial nerve. Other causes of granulomatous inflammation such as Crohn's disease and sarcoidosis must be excluded. On histology, epithelioid cell granulomas and tissue edema are characteristically observed, but may not always be present.

The etiology of OFG is unknown. Several etiologies have been suggested, including infection, genetic predisposition,

and allergy. Patch testing data is limited. A large retrospective study of patch test results demonstrated positive patch testing in 30 % of patients with OFG [5]. The most common allergens involved benzoic acid (found in food preservatives), fragrance, and cinnamon [26, 27, 29]. An 8-week study of a cinnamon- and benzoate-free diet demonstrated significantly decreased oral inflammation in OFG patients [28]. A comprehensive literature search showed the cinnamon- and benzoate-free diet has been shown to provide benefit in at least half of OFG patients, with one in four requiring no other adjunctive therapies for disease resolution [27]. Of note, a negative or positive patch test result to cinnamaldehyde or benzoates did not predict dietary outcome [27] (Table 1, E).

Contact Cheilitis

Xerosis is the most frequent cause of simple cheilitis; however, contact allergy is an important consideration in recalcitrant cheilitis. A retrospective review found 21 of 129 (16.3 %) cases of cheilitis were diagnosed as irritant contact cheilitis [31]. Many potential allergens come into contact with the lips complicating the role of the allergist. Topical medications, sunscreens, dental materials, lipsticks, lip-chap ointments, hygiene products, and other cosmetics should be investigated by patient history. Nearly nine out of ten patients with allergic contact cheilitis are female. Clinical signs include dryness, edema, and crusting.

The recent literature demonstrates that in patients with cheilitis, 25 to 85 % have positive patch testing [5, 31]. Between 20 and 65 % were shown to have clinically relevant patch testing [5, 31]. Most common allergens include fragrances, benzoate, nickel, and dodecyl gallate, in food preservatives and oral hygiene products (Table 1, F) [5, 30–32]. Treatment of contact cheilitis is to remove the allergen or irritant exposure. Topical tacrolimus and topical corticosteroids can also be utilized.

Secondary Burning Mouth Syndrome

Burning mouth syndrome (BMS) is a diagnosis of exclusion characterized by a persistent, burning sensation of the mouth. Symptoms are often present on the tongue, distributed bilaterally, and occasionally associated with xerostomia and dysgeusia [59]. BMS has repeatedly been shown to be common in women over the age of 50 [59–62]. The etiology is unknown, but several mechanisms have been proposed with hormonal, psychiatric, and neuropathic bases [63–65]. Allergic factors seem to be of minor relevance in most cases of BMS, but contact allergy may play a role in secondary burning mouth syndrome.

A large study demonstrates that in patients with burning mouth syndrome, 40 % have positive patch testing [5, 33]. Sixty percent were shown to have clinically relevant patch

testing [5]. The most common allergens were potassium dicyanoaurate, nickel sulfate hexahydrate, gold sodium thio-sulfate, palladium chloride, and fragrance mix [5, 33]. Another study found BMS to have clinically relevant contact allergies to gold and nickel, and following replacement of the metal-containing dental amalgams, the patients experienced symptom resolution [33, 66] (Table 1, G).

Plasma Cell Gingivitis—Atypical Gingivitis

Plasma cell gingivitis is a rare, unique pattern of inflammation of gingival tissue characterized by sharply demarcated, diffuse gingival enlargement, erythema and occasional desquamation. Dark red plaques can be observed. Lesions are typically asymptomatic but a burning sensation may be present. Histologically, a diffuse plasma cell infiltrate extends into the gingiva.

The pathogenesis of plasma cell gingivitis is a type IV hypersensitivity to food flavoring, toothpaste, chewing gum, or other allergens (Table 1, H). The original description occurred in a nearly 40-year-old report in which 11 of 16 (68.8 %) cases of plasma cell gingivostomatitis had exposure to chewing gum and 2 of 16 (12.5 %) patients had complete disease resolution following chewing gum avoidance [34]. The reported association between chewing gum and plasma cell gingivostomatitis has decreased but cases are still noted in the recent literature [67–69]. Similar to contact cheilitis, topical tacrolimus and topical corticosteroids can benefit patients in addition to avoidance of the responsible allergen. Many cases are difficult to diagnose and treat as plasma cell gingivitis remains poorly understood.

Conclusion

In conclusion, the identification of oral pathology is challenging. Mucosal disease with an allergic pathogenesis is most often a hypersensitivity reaction with variable symptoms and physical exam findings. Our approach is to distinguish ulcerative from inflammatory disease and subsequently determine its temporal presentation (Fig. 1). Clinical diagnosis requires a history of prior allergen exposure, a delay from exposure to clinical findings, and improvement following allergen removal. The past decades have seen great contributions to the literature of oral disease; however, future investigations are needed to refine the diagnosis and management of these challenging conditions.

Compliance with Ethical Standards

Conflict of Interest Drs. Kohorst, Bruce, and Torgerson declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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