

Multiple Red Plaques with Severe Burning and Soreness on the Tongue

Hardeep Chehal, BDS; Donald M. Cohen, DMD, MS, MBA;
Indraneel Bhattacharyya, DDS, MSD



The following Case Challenge is provided in conjunction with the American Academy of Oral and Maxillofacial Pathology.

Case Summary

A 68-year-old African-American female presented with very painful lesions of the dorsum and ventral surfaces of the tongue she had endured for at least six months.

After you have finished reviewing the available diagnostic information, make the diagnosis.

Diagnostic Information

History of Present Illness

The patient presented with a chief complaint of burning tongue lesions existing for at least six months. She reported the lesions wax and wane and are aggravated by spicy foods, citrus, or acidic substances such as sodas, vinegar, and lemonade. Episodically her tongue is excruciatingly sore to the extent she is unable to touch the lesions. She also complained of a tingling of her extremities.

Past Medical History

The patient's medical history was significant for breast cancer, treated 30 years ago, and a history of hypertension and asthma. Her medications include prednisone and steroid-based bronchodilators. She is a non-smoker and denies any alcohol use.

Clinical and Cytologic Findings

Intraoral examination revealed multiple red plaques with edema (Figures 1 and 2). Exquisite tenderness was encountered on palpation of the



Figure 1. The anterior ventral and tip of the tongue exhibiting a well demarcated and prominent erythema.



Figure 2. The dorsum and lateral borders of the tongue also demonstrating patchy erythema.

lesional areas of the ventral and dorsal surfaces of her tongue. The redness was particularly prominent on the ventral surface. The dorsal lesions were seen bilaterally. All other oral tissues appeared to be unaffected by the process. Her oral hygiene was excellent. A cytologic smear was taken and failed to reveal any fungal organisms.

Laboratory Findings

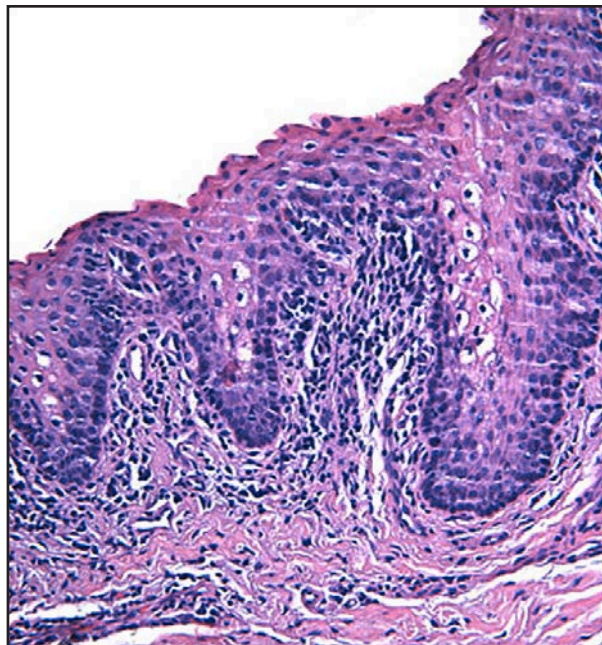
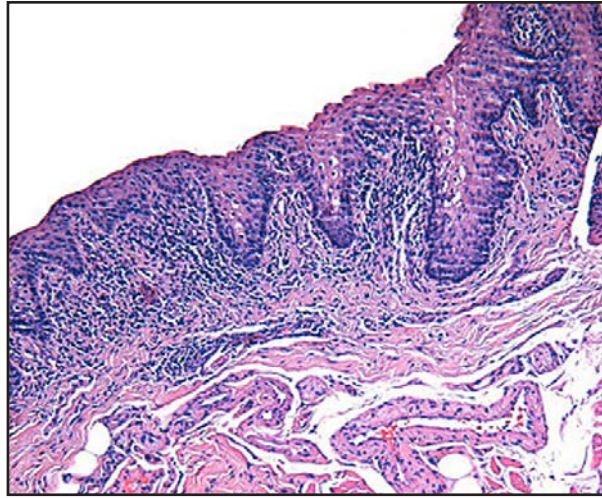
Complete blood work up was done with most findings within the normal range as shown in Table 1.

Histopathological Findings

Microscopic examination of the biopsy specimen showed keratinized stratified squamous epithelium on the surface which was focally atrophic with areas of inflammatory cell infiltration. A moderately dense band of lymphocytes was noted immediately subjacent to the epithelium. Minor atypical changes were seen in the basal layers of the epithelium (Figures 3 and 4). No dysplasia or malignant features were noted. A second biopsy specimen was obtained for direct immunofluorescent antibody staining which revealed fibrinogen positivity along the basement membrane zone. IgG, C3, IgM, and IgA immunohistochemical studies proved to be negative. A diagnosis of chronic lichenoid mucositis with epithelial atrophy suggestive of a lichenoid reaction was rendered.

Table 1. Blood work up.

| Test | Value | Range |
|---|--------|------------------------|
| Vitamin B ₁₂ | L 55 | (243-894) pg/ml |
| Folate | 15.6 | (4.4-19.9) ng/ml |
| Complete Blood Count (with differential count) | | |
| WBC | 5.8 | (5.0-10.0) thou/cu mm |
| RBC | 4.43 | (4.0-5.0) g/dl |
| HGB | 13.3 | (12.0-15.0) g/dl |
| HCT | 40.9 | (36.0-45.0) % |
| MCV | 92.4 | (80.0-100.0) cu micron |
| MCH | 30.0 | (27.0-31.0) pg |
| MCHC | 32.4 | (32.0-37.0) g/dl |
| RDW | H 16.0 | (11.5-14.5) % |
| PLT | 263 | 9150-400) thou/cu mm |
| MPV | 9.2 | (7.4-10.4) fl |
| NEUT | L 57.1 | (60-75) % |
| LYMPH | 34.9 | (25-40) % |
| MONO | 6.2 | (3.7) % |
| EOS | L 1.7 | (3.5) % |
| BASO | 0.1 | (0-1) % |
| Differential Type (automatic differential) | | |
| NEUT ABS | 3.3 | (3.0-7.5) thou/cu mm |
| LYMPH ABS | 2.0 | (1.3-4.0) thou/cu mm |
| MONO ABS | 0.4 | (0.2-0.7) thou/cu mm |
| EOS ABS | 0.1 | (0.1-0.5) thou/cu mm |
| BASO ABS | 0.0 | (0.0-0.1) thou/cu mm |
| Abnormal parameters are indicated by "L" for below normal range and "H" for above normal range. | | |



Figures 3 and 4. Histomicrographs using hematoxylin and eosin stain demonstrating keratinized surface epithelium with focal areas of atrophy and areas of inflammatory cell infiltration. A dense band of lymphocytes is seen immediately subjacent to the epithelium. Minor atypical changes were seen in the basal layers of the epithelium. Images are x10 and x20 magnification, respectively.

Can you make the diagnosis?

A 68-year-old African-American female presented with very painful lesions of the dorsum and ventral surfaces of the tongue she had endured for at least six months.



Select the Correct Diagnosis

- A. Squamous Cell Carcinoma
- B. Benign Mucous Membrane Pemphigoid
- C. Erythematous Candidiasis
- D. Chronic Friction/Trauma-related Lesions
- E. Pernicious Anemia

Squamous Cell Carcinoma

Choice A. Sorry, this is not the correct diagnosis.

Squamous cell carcinoma tends to be an ulcerated lesion with the preferential oral sites of involvement being the tongue and floor of the mouth.¹ Occasionally carcinomas may present simply as a red patch or true erythroplakia particularly in high risk locations such as this one.

Carcinomas of the tongue account for more than 50% of all cases of intraoral squamous cell carcinoma and two thirds of these appear as

painless indurated or ulcerated masses of the posterior lateral border.² The lesion is extremely tender only when the malignancy has invaded deeply into the surrounding tissues and involves neural structures.³ In this case the oral cytologic smears and biopsy would have been abnormal if a cancer was present. The histologic features of carcinoma are highly distinctive and can be recognized readily. Therefore, the clinical presentation and the histologic findings in this case are not compatible with squamous cell carcinoma.

Please re-evaluate the information about this case.

Benign Mucous Membrane Pemphigoid

Choice B. Sorry, this is not the correct diagnosis.

The typical presentation for benign mucous membrane pemphigoid (BMMP) includes ulcers and zones of erythema. Blisters may or may not be seen in conjunction with the zones of erythema. The blisters, when found intact, may contain a clear fluid or sometimes are filled with blood. BMMP may involve any oral surface but is more common on the gingiva. Isolated lesions on the ventral or dorsal tongue are very rare. This patient had no history of blistering or ulceration in the areas of lesional activity. The clinical phenotype known as BMMP is not a single entity but can present with a variety of clinical patterns. Some patients will present with oral lesions alone while others can show involvement of other mucous membranes, the skin, or both. Some variants

may produce widespread mucosal involvement such as scarring of the conjunctiva, erosion, and ulceration of the tracheal and esophageal mucosa, etc. Lesions typically produce pain, dysphagia, and/or peeling of the mucosa. The blisters are only rarely found intact but tend to rupture early leaving irregularly shaped erosions with a yellow fibrinous surface membrane surrounded by an inflammatory halo.

The biopsy specimen is characterized by junctional separation of the epithelium at the level of the basement membrane. This produces a sub-basilar split with a chronic inflammatory infiltrate in the superficial lamina propria that contains eosinophils, lymphocytes, and neutrophils.⁴ The clinical characteristics and the histology of this case do not support the diagnosis of benign mucous membrane pemphigoid.

Please re-evaluate the information about this case.

Erythematous Candidiasis

Choice C. Sorry, this is not the correct diagnosis.

This would be an excellent choice if the cytologic smears taken had been positive for candidal organisms. Candidiasis of the oral mucosa is very common and even more prevalent in patients using steroid medication. Oral candida infection, commonly referred to as candidiasis, is one of the most common conditions affecting the oral mucosa. *Candida albicans* accounts for 70%-80% of the oral isolates. Symptoms may be variable. Some patients may be entirely asymptomatic. Symptomatic patients may have pain

that ranges from mild to intense. Many patients report a painful burning sensation that may cause dysphagia. The lesions in this patient best correspond with the erythematous form of candidiasis, which most often affects the palate and dorsal tongue.⁵

Candidiasis can cause signs and symptoms very similar to those seen in this case and it should be included in the differential diagnosis. However, cytologic smears and histologic examinations normally reveal the presence of pseudohyphae as evidence of candidal involvement.

Please re-evaluate the information about this case.

Chronic Friction/Trauma-related Lesions

Choice D. Sorry, this is not the correct diagnosis.

This is another important entity in the differential diagnosis that can simulate most of the signs and symptoms present in this patient. The mucosa lining of the oral cavity is subject to considerable trauma induced by various local irritants, such as food, biting, cigarettes, alcohol, toothpicks, and dentures. While the oral mucosa has significant tolerance to such insults, damage can be significant enough to produce a reactive lesion. These lesions can be painful. They usually

are self-limiting and regress when the irritant is removed.⁶

In this case the microscopic features argue strongly against this diagnosis. The typical histologic features of traumatic lesions include epithelial hyperplasia with increased keratinization in conjunction with overgrowth of fibrous connective tissue or granulation tissue. These features were not present in the biopsy from this patient.

Please re-evaluate the information about this case.

Pernicious Anemia

Choice E. Congratulations! You are correct!

Discussion

The location and clinical appearance of the lesions, when considered in conjunction with the laboratory studies, are most suggestive of pernicious anemia. The diagnosis was established by correlating these clinical and laboratory findings with the histopathologic features of the submitted specimen. The blood test revealing a markedly decreased vitamin B₁₂ (cobalamin) level of 55pg/ml (normal range 240-900pg/ml) is particularly strong confirmatory evidence.

Pernicious anemia is a specific form of megaloblastic anemia most often affecting older adults. It is caused by atrophic gastritis with resultant failure of intrinsic factor production. The absence of intrinsic factor leads to vitamin B₁₂ deficiency and is characterized by abnormally large red blood cells, gastrointestinal disturbances, and neurologic complications including paresthesias, periphery neuropathy, and combined systems disease (demyelination of dorsal columns and corticospinal tract). Most patients lack intrinsic factor because of an autoimmune destruction of the parietal cells of the stomach, which results in the decreased absorption of cobalamin.⁸ In most cases it takes as long as four to six years of a deficiency state before symptoms are manifested. Some of the common clinical features include fatigue,

weakness, shortness of breath, paresthesia, and tingling or numbness of the extremities. Oral manifestations include pain, burning sensation, and altered sense of taste. The symptoms are generally confined to the tongue but may extend to other parts of the oral mucosa. The tongue appears erythematous and atrophic. The glossodynia associated with pernicious anemia can undergo spontaneous remission but invariably recurs.⁹

Oral supplementation with vitamin B₁₂ does not help due to the lack of intrinsic factor necessary for proper absorption of the agent. Treatment consists of periodic (usually monthly) intramuscular injections of cyanocobalamin or hydroxocobalamin.¹⁰ This treatment is usually required for the remainder of the patient's life. Initial treatment consists of a dose of 100 mcg daily for six or seven days administered by intramuscular or deep subcutaneous injection. If there is clinical improvement with this treatment, the same amount may be given on alternate days for seven doses, then every three to four days for another two to three weeks. By this time hematologic values should have returned to normal. Monthly injections of 100mcg are then instituted and continued for the remainder of the patient's life. Folic acid should be administered concomitantly, if needed. A new vehicle for drug delivery is now available in the form of a nasal gel (Nascobal, QOL Medical, Kirkland, WA, USA). It is usually administered as a nasal spray at the dose of one spray (500mcg) once a week in one nostril.

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About the Authors

Note: Bio information was provided at the time the case challenge was developed.

Hardeep Chehal, BDS



Dr. Chehal is the Senior Resident in Oral and Maxillofacial Pathology in the Department of Oral and Maxillofacial Surgery and Diagnostic Sciences at the University of Florida College of Dentistry in Gainesville, FL, USA.

E-mail: hchehal@dental.ufl.edu

Donald M. Cohen, DMD, MS, MBA



Dr. Cohen is a Professor in the Department of Oral and Maxillofacial Surgery and Diagnostic Sciences at the University of Florida College of Dentistry in Gainesville, FL, USA. He is the Section Head and Director of the Oral and Maxillofacial Pathology Biopsy Service and Laboratory. He is a Diplomate of the American Board of Oral and Maxillofacial Pathology.

E-mail: dcohen@dental.ufl.edu

Indraneel Bhattacharyya, DDS, MSD



Dr. Bhattacharyya is an Assistant Professor in the Department of Oral and Maxillofacial Surgery and Diagnostic Sciences at the University of Florida College of Dentistry in Gainesville, FL, USA. He is the director of the Oral and Maxillofacial Pathology residency training program. He is also a Diplomate of the American Board of Oral and Maxillofacial Pathology.

E-mail: ibhattacharyya@dental.ufl.edu