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Case Challenge
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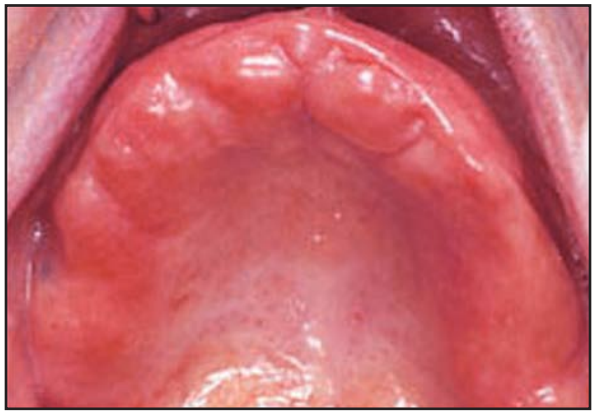
Persistent Oral Tenderness

Cynthia L. Kleinegger, DDS, MS



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

Case Summary

This case challenge presents a patient with erythematous palatal mucosa.

An 81-year old male presents with a chief complaint of oral soreness, primarily involving the tongue and denture-bearing mucosa. Symptoms have been present for approximately two months and have not been relieved by denture adjustments.

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

Diagnostic Information

Additional Clinical History

Review of the patient's medical history reveals he had been diagnosed with Crohn's disease 16 years previously. Two weeks ago he completed a course of prednisone prescribed to manage an exacerbation of Crohn's disease. His current medications are dicyclomine hydrochloride, an anticholinergic agent, and mesalamine, an antiinflammatory agent, both for the management of this gastrointestinal disease. He also takes calcium and folic acid supplements.

Review of the patient's dental history reveals he has worn a maxillary complete denture and a mandibular complete overdenture for 3 years. He has complained frequently of localized areas of soreness; however, in the past these have been relieved by minor denture adjustments.

Clinical Findings

Head and neck examination reveals no visible extraoral abnormalities and no palpable lymphadenopathy. Intraoral examination reveals moderate to severe erythema of the palatal and alveolar mucosa. (Figures 1, 2, and 3) The dorsal tongue exhibits moderate erythema with atrophy of the filiform papillae. (Figure 4) The intraoral soft tissues appear dry and manipulation of the major salivary glands reveals minimal salivary flow.

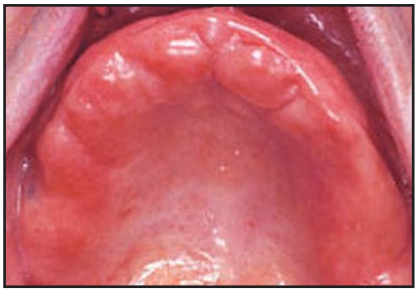


Figure 1. Erythematous palatal mucosa

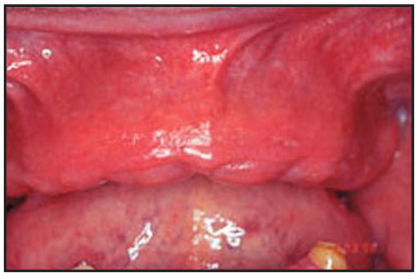


Figure 2. Erythematous maxillary alveolar mucosa

Photomicrographs

A cytologic preparation stained with periodic acid-Schiff stain reveals numerous fungal hyphae and occasional ovoid yeast forms. (Figure 5)

Laboratory Studies

The patient reports he has recently undergone a complete physical examination including blood studies.

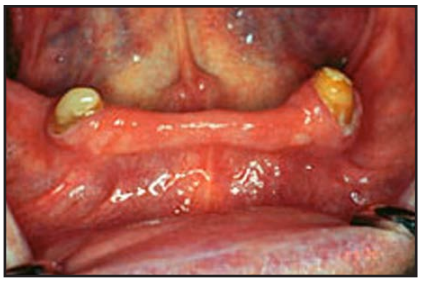


Figure 3. Erythematous mandibluar alveolar mucosa

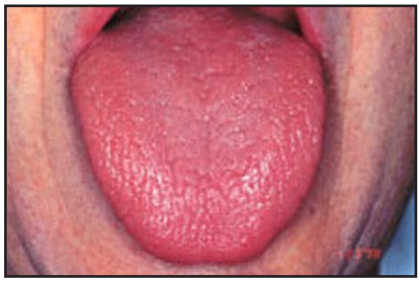


Figure 4. Erythema and atrophy of fillform papillae of the dorsal tongue

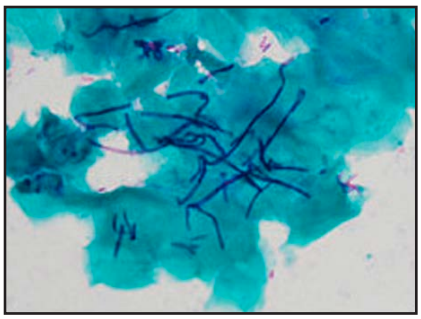


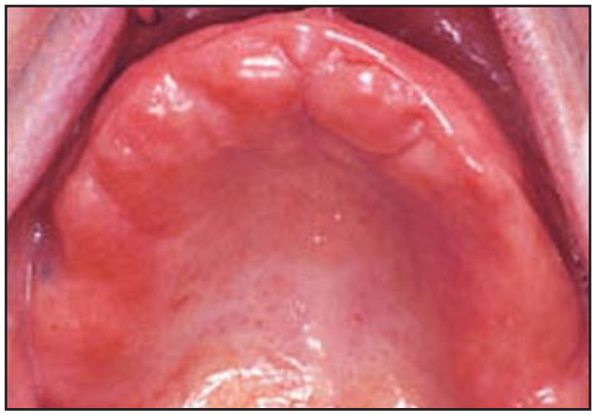
Figure 5.

Table 1. Blood Studies

Test	Results	Normal Range
Hemoglobin	15 g/dL	14-18 g/dL
Hematocrit	43%	40-52%
Red blood cell count	5.1 x 10^{12}/L	4.5-6.2 x 10^{12}/L
Mean cell volume	84 fL	80-94 fL
Mean cell hemoglobin	30 pg	27-32 pg
Mean cell hemoglobin concentration	33 g/dL	32-36 g/dL
White blood cell count	6.2 x 10^{9}/L	5-10 x 10^{9}/L
Neutrophils	55%	40-60%
Lymphocytes	37%	20-40%
Eosinophils	2%	1-3%
Basophils	0%	0-1%
Monocytes	6%	4-8%
Platelet count	0.28 x 10^{12}/L	0.15-0.4 x 10^{12}/L
Vitamin B_{12}	390 pg/mL	>200 pg/mL
Folic acid	18 pg/mL	2-20 ng/mL
Fasting blood glucose	88 mg/dL	65-110 mg/dL
Iron	94 mg/dL	50-175 mg/dL
Iron binding capacity	334 mg/dL	250-410 mg/dL

Can you make the diagnosis?

This case challenge presents a patient with erythematous palatal mucosa.



Select the Correct Diagnosis

A. Contact Allergy to Denture Acrylic
B. Pernicious Anemia
C. Candidiasis
D. Idiopathic Burning Mouth Syndrome
E. Oral Manifestations of Crohn's Disease

Contact Allergy to Denture Acrylic

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

Allergy to denture base acrylic is extremely uncommon. Irritation may occur due to the leaching of monomer from incompletely cured acrylic and, therefore, occurs immediately after denture delivery.[1,2] The patient in this case had been wearing his current prostheses for over 3 years.

Please re-evaluate the information on this case and make another selection.

Pernicious Anemia

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

Although pernicious anemia often presents with atrophic glossitis and/or generalized mucositis and is a predisposing factor for candidiasis, the normal blood studies in this case would rule out that diagnosis.[3,4] The diagnosis of pernicious anemia depends on an abnormally low serum vitamin B12level. Hemoglobin, hematocrit, and red blood cell counts are usually decreased and, unless there is a concomitant iron deficiency anemia, the mean red cell volume is usually markedly elevated. Since pernicious anemia affects all blood cell lines, white blood cell and platelet counts may be decreased.[5]

In addition to glossitis or generalized mucositis, oral symptoms of pernicious anemia may include perioral paresthesia. Patients may also report tingling or numbness of the extremities or other systemic symptoms such as fatigue, weakness, shortness of breath, loss of appetite, and diarrhea.[3,5]

Please re-evaluate the information on this case and make another selection.

Candidiasis

Choice C. Congratulations! You are correct.

This patient exhibited clinical, historical, and cytologic features consistent with candidiasis.

Discussion

Candidiasis (*candidosis*) is a common oral fungal infection, usually caused by *Candida albicans*. *C albicans* is present as part of the normal oral flora in 40% to 60% of people.[6,7] Although less common, other *Candida species* including *C glabrata*, *C tropicalis*, *C guilliermondi*, and *C krusei* have been isolated from the oral cavity both as commensals and pathogens.[8,9]

Local and systemic factors that predispose an individual to develop *candidiasis* include xerostomia, intraoral prosthetic devices, other mucosal diseases, broad-spectrum antibiotic use, immunocompromising diseases, medical treatments, nutritional deficiencies, and metabolic disorders.[4,6,7,9] (Table 2)

Clinical Presentation of *Candidiasis*

Oral *candidiasis* has three major variants based on clinical appearance: erythematous (also known as atrophic), pseudomembranous, and hyperplastic.[6,7,9,11] While the erythematous and pseudomembranous variants may be associated with a burning sensation, typically the hyperplastic form and the atrophic form associated with

Table 2. Predisposing Factors for *Candidiasis*

Local Factors

• Xerostomia
  ○ Drug induced
  ○ Sjögren's disease
• Head and neck radiation therapy
• Mucosal disease
• Oral Prostheses
  ○ 24-hour use
  ○ Ill-fitting
  ○ Poor hygiene
• Topical or inhalation corticosteroid therapy

Systemic Factors

• HIV disease
• Leukemia
• Endocrine disorders
  ○ Diabetes mellitus
  ○ Hypothyroidism
• Nutritional deficiency
  ○ Iron
  ○ Vitamin B_{12}
  ○ Folic acid
• Drug therapy
  ○ Cancer chemotherapy
  ○ Antibiotic therapy
  ○ Corticosteroid therapy
  ○ Immunosuppressive drugs
• Radiation therapy

denture stomatitis are asymptomatic. Other complaints that may be reported by patients with *candidiasis* include a scalded feeling, irritation from spicy or acidic foods and beverages, surface roughness, sore throat, and altered taste or smell.[6]

As the name implies, erythematous candidiasis presents with primarily or exclusively erythematous mucosa. Erythematous candidiasis may occur as an acute or chronic infection. Chronic atrophic candidiasis is often observed on denture-bearing mucosa. It is typically associated with 24-hour denture wear, ill-fitting dentures, or poor denture hygiene. When associated with a maxillary denture, the chronically inflamed palatal mucosa may also exhibit inflammatory papillary hyperplasia. (Figure 6) Atrophic candidiasis of the tongue manifests as localized or generalized erythema with loss of the filiform papillae.

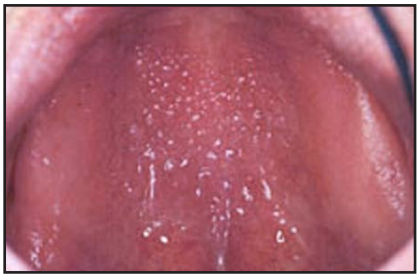


Figure 6. Inflammatory papillary hyperplasia.

Pseudomembranous *candidiasis*, also known as thrush, is the most easily recognized form of candidiasis. It presents with soft white plaques that can be rubbed off with minimal to moderate pressure, revealing an erythematous base. (Figure 7)

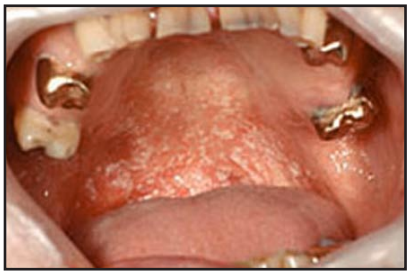


Figure 7. Pseudomembranous cadidiasis involving the palatal mucosa.

Chronic hyperplastic *candidiasis* presents as focal white or speckled red and white patches that are adherent. This variant is uncommon and is most often found on the buccal mucosa, especially the commissural area. (Figure 8) Smoking has been implicated as a risk factor for hyperplastic candidiasis.[6,10] Based on the clinical appearance alone, hyperplastic *candidiasis* cannot be distinguished from other white lesions such as focal keratosis, epithelial dysplasia, or carcinoma *in situ*. A lesion clinically diagnosed as hyperplastic *candidiasis* must be biopsied if it does not respond to initial antifungal therapy.

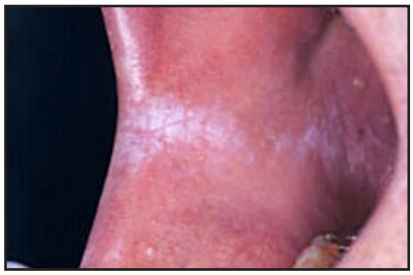


Figure 8. Hyperplastic candidiasis involving the buccal mucosa.

Two other clinical entities associated with *Candida* are angular cheilitis and median rhomboid glossitis. A patient with angular cheilitis exhibits fissured, erythematous, often crusty areas at one or both commissures of the lips. (Figure 9) Angular cheilitis is often seen in persons with decreased vertical dimension of occlusion. It may be itchy or painful and may bleed when the mouth is opened wide. Patients with *Candida-related* angular cheilitis may exhibit intraoral *candidiasis*. Median rhomboid glossitis is a flat or raised, red, depapillated area in the mid-dorsal tongue. (Figure 10) It is usually asymptomatic, but may be associated with discomfort. Median rhomboid glossitis may resolve with antifungal therapy, but it commonly recurs when treatment is discontinued.

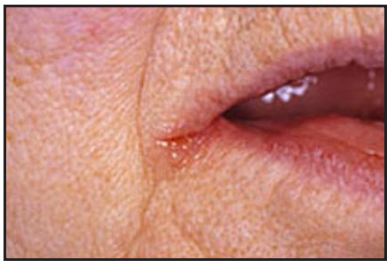


Figure 9. Angular chellitis

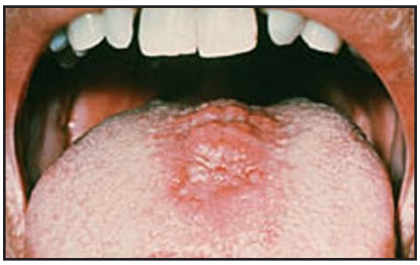


Figure 10. Median fhomboid glossitis

Diagnosis of *Candidiasis*

The diagnosis of *candidiasis* is best made by combining clinical and laboratory findings.[7] Clinical suspicion of *candidiasis* may be confirmed with cytologic preparations. This is easily performed by scraping the edge of a moistened tongue blade, plastic instrument, or cement spatula over the involved oral mucosa. The material obtained is spread evenly on a glass microslide. The microslide is then immersed in 95% ethanol or sprayed with cytologic fixative to preserve the cells. In the laboratory, a periodic acid-Schiff stain allows the fungal organisms to be visualized microscopically. (Figure 5)

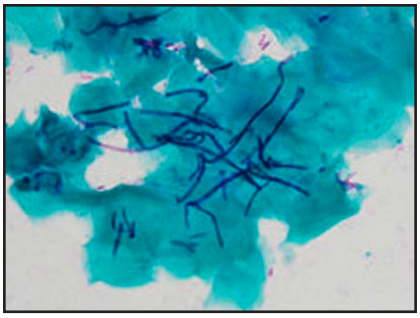


Figure 5.

While biopsy is not generally indicated to diagnose *candidiasis*, it may be necessary to distinguish erythematous and *hyperplastic candidiasis* from other lesions such as epithelial dysplasia or carcinoma *in situ*. On biopsy, *hyperplastic candidiasis* will exhibit yeast and hyphae invading the keratin and upper spinous layers.[9,10] Special stains such as periodic acid-Schiff or methenamine silver may be necessary to demonstrate fungal organisms. (Figure 11) The epithelium in *hyperplastic candidiasis* may exhibit some degree of epithelial dysplasia.[9] It is not possible to determine whether the dysplastic changes have been induced by the candidal infection, or if the yeast has infected an otherwise dysplastic epithelium.

Close follow-up of such lesions is essential and repeat biopsy may be necessary, if they persist following antifungal therapy.

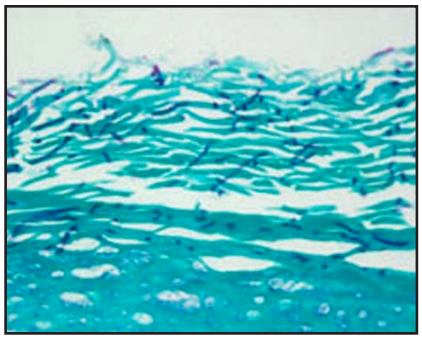


Figure 11. This biopsy specimen of *hyperplastic candidiasis* stained with periodic acid-Schiff reveals purple fungal hyphae invading the epithelium, which is counterstained green.

Treatment of *Candidiasis*

A variety of topical and systemic medications is available for treatment of *candidiasis*. (Table 3) Most cases of *candidiasis* confined to the oral cavity may be treated effectively with topical antifungal agents. Patients who do not respond to or have difficulty complying with a topical regimen may require systemic therapy.

Systemic ketoconazole is associated with many drug interactions and hepatic effects, which prevents its use in some patients.[6,9] Fluconazole is more expensive but has fewer side effects and drug interactions. Itraconazole oral solution is approved for oral and esophageal candidiasis and may be more effective in some patients who have not responded to fluconazole.[12]

Since these systemic antifungal agents are all associated with numerous drug interactions, they should be prescribed in consultation with the patient's physician as appropriate. Fluconazole and ketoconazole are contraindicated in patients taking terfenadine and cisapride. Ketoconazole is also contraindicated in patients taking astemizole or triazolam. Co-administration of itraconazole is contraindicated in patients taking terfenadine, cisapride, astemizole, triazolam, midazolam, lovastatin, and simvastatin.

In the general population, antifungal drug resistance is uncommon. Fluconazole, ketoconazole,

Table 3. Management of Oral *Candidiasis*

Medication	Dosage and Directions[1]
chlorhexidine 0.12% oral rinse (Peridex, PerioGard, generic)[2] or 0.2% alcohol-free aqueous[3]	15 ml mouthrinse and expectorate TID. NPO 1/2 hr after use.
nystatin oral suspension 100,000 units/ml[4]	5 ml mouthrinse 1 min and expectorate[5] QID (PC and HS). NPO 1/2 hr after use.
clotrimazole 10 mg/ml suspension[6]	Swab 1-2 ml on affected area QID (PC and HS). NPO 1/2 hr after use.
ketoconazole 2% cream (Nizoral) or clotrimazole 1% cream (Lotrimin)	Apply thin film to inner surface of denture(s) and/or corners of mouth QID (PC and HS). NPO 1/2 hr after use.
clotrimazole 10 mg oral troches (Mycelex)	Dissolve 1 troche slowly in mouth 5x daily. NPO 1/2 hr after use.
ketoconazole 200 mg tablets (Nizoral)	1 tablet PO QD for 7 to 10 days. Do not take antacids within 2 hr of this medication.[7]
fluconazole 100 mg tablets (Diflucan)	1 tablet PO BID for first day, then 1 tablet PO QD for 10 to 14 days.
itraconazole 10 mg/ml oral solution (Sporanox)	10 ml mouthrinse and swallow BID.[7,8]

PC = post cibos (after meals)
HS = hori somni (at bedtime)

1. Adult dosages. In most patients decreased frequency and dosages may be used if maintenance therapy is required.
2. May be useful for disease prevention but not a first line drug for treatment. High alcohol content (11.6%) will irritate mucosa and enhance xerostomia. Should not be prescribed for recovering alcoholics.
3. Must be prepared by experienced compounding pharmacist. Many formulas include flavorings that decrease efficacy.
4. High sucrose content.
5. May be swallowed for pharyngeal involvement.
6. Compounded in confectioners glycerin.
7. Acidic environment is required for absorption.
8. Should be taken without food for maximum bioavailablility.

and itraconazole resistance have been well documented in HIV-positive populations.[6,12,13] Antifungal drug resistance appears to be more common among *non-albicans Candida*.[12] In cases of *candidiasis* refractory to initial drug therapy, fungal culture and drug susceptibility testing should be performed to guide further treatment.

An important part of the management of *candidal infection* is identification of the patient's predisposing factor(s). Should available history and clinical examination fail to reveal a predisposing factor, further evaluation for a possible underlying cause is indicated.[7] This is particularly important in the case of recurrent or persistent *candidiasis*.

When possible, predisposing factors should be removed or controlled. Since this is often not feasible, maintenance antifungal therapy may be required. (Table 3)

Patients with denture-related *candidiasis* should be educated regarding proper denture use. Prostheses should be evaluated and replaced if necessary. Soaking in 0.12% chlorhexidine gluconate or 1:50 sodium hypochlorite has been recommended to disinfect dentures.[11,14] Denture disinfection may also be accomplished by using the denture to deliver an antifungal cream or ointment to the infected denture-bearing mucosa. (Table 3) Even when asymptomatic, *candidiasis* of denture-bearing mucosa should be treated, as inflamed mucosa provides poor support and inflammation may contribute to resorption of underlying bone.[4] In addition, untreated palatal *candidiasis* may progress to inflammatory papillary hyperplasia, which may require surgical removal.[2]

The patient in this case exhibited clinical and historical features of erythematous *candidiasis*, confirmed by the presence of fungal hyphae on cytologic preparations. The predisposing factors for *candidiasis* identified in this patient were xerostomia secondary to the use of the anticholinergic drug dicyclomine hydrochloride and immunosuppression due to a recent course of prednisone. The infection was treated with ketoconazole 2% cream applied to the inner surface of the dentures four times daily. (Table 3) Since continued use of dicyclomine hydrochloride was necessary for management of Crohn's disease, the patient's xerostomia could not be eliminated. Following resolution of signs and symptoms of *candidiasis*, the frequency of topical ketoconazole use was gradually decreased to a maintenance frequency of once daily. The patient was also educated in self-management of xerostomia.

Idiopathic Burning Mouth Syndrome

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

Burning mouth syndrome is a diagnosis of exclusion and would be inappropriate in view of this patient's cytologic findings. Most patients with burning mouth syndrome exhibit no visible soft tissue changes.[15,16]

Please re-evaluate the information about this case.

Oral Manifestations of Crohn's Disease

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

Although oral lesions of Crohn's disease may correlate with exacerbation of intestinal symptoms, the mucosal changes exhibited by this patient were not consistent with the oral manifestations of this disease. Oral lesions of Crohn's disease include a cobblestone pattern of the buccal mucosa, linear hyperplastic folds and ulcers of the vestibules, and diffuse firm swelling of the lips. The gingiva may exhibit granular, erythematous swellings and aphthous-type ulcerations may be present.[17]

Please re-evaluate the information about this case.

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About the Author

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

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