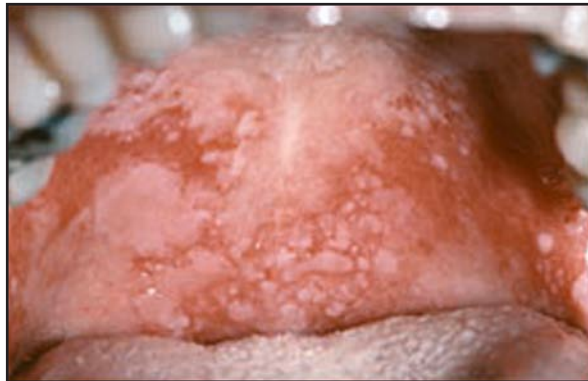


## Multiple Painful Oral Ulcers

**Michele Ravenel, DMD; Brad W. Neville, DDS; James Tankersley, DMD**



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

### **Case Summary**

A 66-year old white male was referred with a chief complaint of multiple painful oral and pharyngeal ulcerations. He stated his symptoms began four months earlier with the occurrence of a mild sore throat, which was followed by the development of numerous ulcers throughout the rest of his mouth. Because of the pain from these lesions, the patient suffered from dysphagia and resultant weight loss.

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

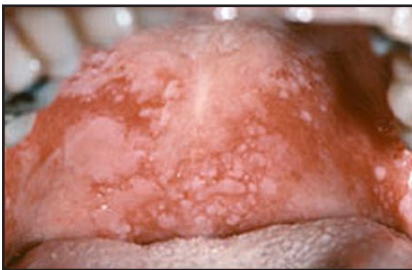
## Diagnostic Information

### Medical History

Before the onset of his oral lesions, the patient was in excellent health. He had a 25 year history of gout for which he used diclofenac as needed. He also used celecoxib for joint pain in his knees.

### Oral Findings

The patient had multiple irregular ulcerations of the posterior hard and soft palate, buccal mucosa, floor of mouth, and gingiva. (Figures 1-4) The superficial layer of the mucosa could be peeled away when firm lateral pressure was applied (positive Nikolsky sign).



**Figure 1.** Widespread ulcerations of the soft palate.



**Figure 2.** Vesiculoerosive lesions of the right buccal mucosa.



**Figure 3.** Diffuse ulcerations along the marginal gingiva.



**Figure 4.** Erosions of the floor of the mouth.

### Other Clinical Findings

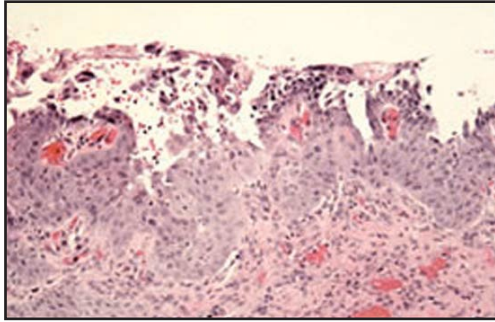
The patient also complained of tender, crusted ulcerations involving the left ear canal and nares. He denied the presence of any ocular or genital lesions. However, he did report the recent development of red splotches on his chest and an ulceration on his back. (Figure 5)



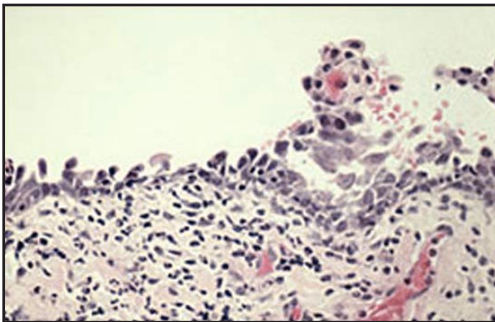
**Figure 5.** Ruptured vesicle on the patient's back.

### Incisional Biopsy and Photomicrographs

An incisional biopsy was obtained from the edge of one of the ulcers, including some normal-appearing adjacent tissue. The mucosa was partially covered by stratified squamous epithelium, which showed loss of cohesion of the spinous epithelial cells (acantholysis). (Figure 6) The superficial epithelial layers were missing throughout much of the specimen, leaving behind one to several layers of basilar epithelial cells resembling a "row of tombstones." (Figure 7) Rounded acantholytic cells ("Tzanck cells") could be found above the attached basilar cells.



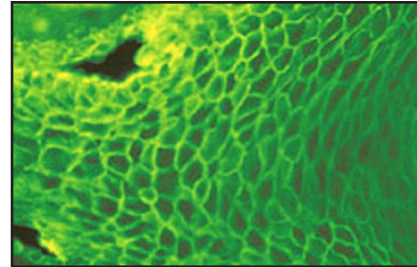
**Figure 6.** Medium power photomicrograph showing suprabasilar blister formation with loss of the superficial layers of the epithelium. The cells of the spinous layer show loss of cohesion (acantholysis) and float freely within the blister area.



**Figure 7.** High power photomicrograph showing loss of the upper epithelium with a remaining layer of basilar epithelial cells that resembles a "row of tombstones."

### Immunofluorescence Studies

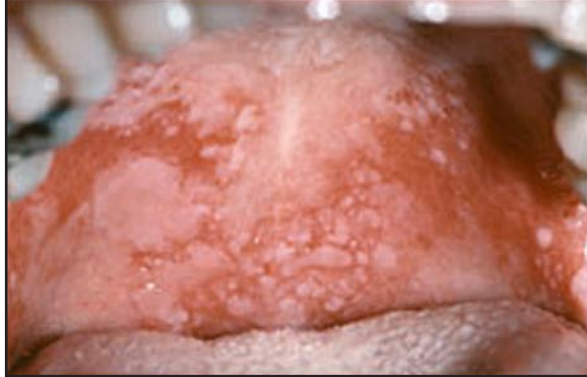
Additional biopsy material from an uninvolved site was transported in Michel's fixative (Poly Scientific, Bay Shore, NY 11706), frozen, and prepared for direct immunofluorescence studies. This specimen was positive for both IgG and C3 in the intercellular spaces between the spinous epithelial cells. (Figure 8)



**Figure 8.** Direct immunofluorescence highlights the presence of IgG in the intercellular spaces between the spinous epithelial cells.

### Can you make the diagnosis?

A 66-year old white male was referred with a chief complaint of multiple painful oral and pharyngeal ulcerations.



### Select the Correct Diagnosis

- A. Erythema Multiforme
- B. Erosive Lichen Planus
- C. Major Aphthous Ulcers
- D. Pemphigus Vulgaris

## Erythema Multiforme

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

Erythema multiforme is a vesiculobullous disease of unknown etiopathogenesis which affects both the skin and mucous membranes. In about half of the cases a preceding infection (herpes simplex, *Mycoplasma pneumoniae*) or exposure to a medication can be identified. Patients are most frequently in their twenties or thirties, and men are affected more often than women. Prodromal symptoms of fever, headache, sore throat, and malaise may precede clinical signs of the disease.

In the oral cavity, erythematous patches undergo necrosis and form irregular areas of erosion and ulceration. A diffuse distribution is seen, although the hard palate and gingivae may be spared. Hemorrhagic crusting of the vermilion border is

a characteristic finding. Skin lesions develop in 50% of patients and are variable in appearance. Sometimes, these skin lesions present as highly characteristic concentric, erythematous rings that resemble a target or bull's eye. Unlike the gradual and progressively worsening nature of the lesions in this case, erythema multiforme typically has a sudden, explosive onset.

Histopathologic features of erythema multiforme may include subepithelial or intraepithelial vesiculation with necrotic keratinocytes and a mixed perivascular inflammatory infiltrate. Although blister formation does occur, acantholysis of the spinous cells is not found. The histopathologic features are often non-specific, and the diagnosis may be based on clinical appearance and the exclusion of other vesiculobullous diseases.<sup>1-4</sup>

Please re-evaluate the information about this case.

## Erosive Lichen Planus

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

Lichen planus is a common mucocutaneous disease of unknown etiology which most often affects middle-aged and older adults. Women are affected twice as frequently as men. There are two general forms of lichen planus: reticular and erosive. The classic presentation of reticular lichen planus is an interlacing network of keratotic white lines (Wickham's striae) that tend to wax and wane. The reticular form most frequently involves the buccal mucosa, tongue, and gingivae. It is often asymptomatic and treatment may not be required. Erosive lichen planus appears as atrophic, erythematous areas with varying degrees of central ulceration. Peripheral radiating white striae may be present. Because of the erythematous component and similarities to other vesiculobullous diseases, biopsy is often

required to confirm the diagnosis. The lesions are frequently symptomatic and require treatment with topical corticosteroids.

Skin lesions have been reported to develop in as many as 20-40% of patients with oral lichen planus. These lesions usually affect the flexor surfaces of the extremities and appear as purple, pruritic, polygonal papules.

Histopathologic findings include varying degrees of hyperorthokeratosis and hyperparakeratosis, thickening of the spinous layer, "saw-toothed" rete ridges, hydropic degeneration of basal cell layer, and necrotic keratinocytes ("Civatte bodies"). An intense band-like infiltrate of T-lymphocytes is seen subjacent to the epithelium. Some cases will show an irregular separation of the epithelium from the connective tissue, but intraepithelial blister formation with acantholysis does not occur.<sup>5-8</sup>

Please re-evaluate the information about this case.

## Major Aphthous Ulcers

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

Recurrent aphthous ulcerations are common lesions that affect approximately 20% of the population. The exact cause of aphthae is unknown, but the lesions appear to represent local immunologic destruction of the mucosa which is mediated by T-lymphocytes. Various “triggers” may stimulate development of these ulcers including stress, local trauma, food allergies, and hormonal changes.

Three clinical variations of aphthous ulcerations are seen. Minor aphthous ulcers are small (3-10 mm) and appear in clusters of one to five lesions. They arise on non-keratinized mucosa and resolve without scarring in seven to 14 days. The lesions appear as small round or ovoid ulcerations that are covered by a fibrinopurulent membrane and surrounded by an erythematous halo. They rarely affect keratinized tissue and the rate of recurrence is variable.

Major aphthous ulcerations are larger (> 1 cm), deeper lesions that persist for up to six weeks and heal with scarring. They can affect any area of the oral cavity and the recurrence rate is variable. Dehydration, malnutrition, and secondary infection are potential complications.

Herpetiform aphthous ulcerations are small (< 3 mm) and affect both keratinized and non-keratinized tissue. They appear in clusters of up to 100, heal in seven to ten days, and recur frequently. Because of their clinical appearance, they are sometimes mistakenly identified as herpes simplex lesions.

On microscopic examination, aphthous ulcers demonstrate a central zone of ulceration covered by a fibrinopurulent membrane. The underlying connective tissue exhibits increased vascularity and a mixed inflammatory cell infiltrate. Unlike the current case, aphthous ulcers do not demonstrate vesicle formation and acantholysis. Because the histopathology is non-specific, the diagnosis is made by the clinical history and exclusion of other oral ulcerative diseases.<sup>9-11</sup>

Please re-evaluate the information about this case.



## Pemphigus Vulgaris

### Choice D. Congratulations! You are correct.

Pemphigus is a group of autoimmune blistering diseases affecting both the skin and mucosa. Pemphigus vulgaris (PV), which accounts for 80% of the reported cases, is a rare and serious condition that can result in death if left untreated. In pemphigus vulgaris, the patient develops auto-antibodies against desmoglein 3 and desmoglein 1 which are structural components of the desmosomes that hold squamous epithelial cells together. As a result of this attack, epithelial splitting and blister formation occur. Onset typically occurs during the fourth through sixth decades of life and affects both men and women equally. There is an increased incidence in Ashkenazi Jews and those of Mediterranean descent.<sup>12-17</sup>

Between 80-90% of patients with PV develop oral ulcers, and these oral lesions are the first sign of the disease in 60% of those affected. Lesions begin as vesicles which rupture quickly and leave superficial, irregular areas of erosion. Intact vesicles are rarely seen. The erosions continue to expand, incorporating larger areas of mucosa. Sites commonly affected include the buccal mucosa, palate, ventral tongue, and gingivae.

Skin lesions usually affect the scalp, face, trunk, and points of pressure. They appear as flaccid bullae which easily rupture leaving erythematous, crusted erosions. The ability to induce cutaneous lesions by applying firm lateral pressure is a classic feature of PV and is termed a positive Nikolsky sign.

Diagnosis is accomplished via biopsy of perilesional tissue. Specimens taken from the center of an erosion are often non-specific histologically. Characteristic histopathologic features include intraepithelial vesicle formation with acantholysis of the spinous cell layer which results in rounded, free-floating Tzanck cells within the blister cleft. If the upper epithelial layers are lost, a row of basilar cells may remain attached to the connective tissue resembling a "row of tombstones." The diagnosis of PV should be confirmed using direct immunofluorescence which will demonstrate a characteristic "fishnet pattern" of autoantibodies (usually IgG or IgM)

and the C3 component of complement within the intercellular spaces. Recently, an enzyme-linked immunosorbent assay (ELISA) has been developed which measures circulating autoantibodies against desmogleins 1 and 3.<sup>17</sup> A study by Harman and others demonstrated a significant association between desmoglein 3 antibody levels and oral disease severity.<sup>18</sup> Early diagnosis and treatment are crucial in the management of PV. Treatment prior to the appearance of cutaneous lesions improves the chance for remission. Systemic corticosteroids remain the cornerstone of treatment for PV. Prior to the advent of modern corticosteroid therapy, PV was usually fatal as a result of secondary infections and electrolyte imbalances. Today the mortality rate is between 5-10%, mostly secondary to complications from long-term high dose corticosteroid therapy.

Typically prednisone is used to gain initial disease control, and once achieved, the dose is decreased to the lowest maintenance dose possible. The use of immunosuppressive adjuvants such as azathioprine or mycophenolate mofetil may allow reduction of the corticosteroid dose and the potential long-term complications of corticosteroid therapy. Pulse therapy refers to the discontinuous intravenous infusion of high dose glucocorticoids over a short period of time in an effort to achieve remission. Other possible adjuvant therapeutic agents include cyclophosphamide, methotrexate, gold compounds, and human intravenous immunoglobulins (HIVIG). Oral lesions have responded to topical application and intralesional injection of glucocorticoids. Plasmapheresis, immunophoresis, and photopheresis may be beneficial in patients refractory to corticosteroid therapy.<sup>19-23</sup>

In the present case, the patient was treated with high-dose prednisone (80 mg daily) in combination with azathioprine. Currently, after two months of therapy, his oral lesions have greatly improved and have mostly resolved. (Figures 9-12) Once total healing has been achieved, the corticosteroid dosage will be tapered to a minimum level necessary to keep the disease under control.

Because oral lesions may precede the development of cutaneous lesions by up to six months, oral practitioners can play an important role in the early diagnosis of pemphigus vulgaris. Timely diagnosis and treatment may minimize disease activity, allow early remission, and limit morbidity from therapy.





**Figure 9.** After two months of therapy with prednisone and azathioprine, the palatal lesions have mostly resolved.



**Figure 10.** Only a small ulceration still persists on the buccal mucosa after two months of therapy.



**Figure 11.** Marked improvement of the gingiva.



**Figure 12.** After two months of therapy, the floor of the mouth has greatly improved, although focal small erosions can still be seen.

## References

1. Silverman S Jr. The bullous desquamative lesions of oral mucosa. *J Calif Dent Assoc.* 2000 Dec; 28(12):928-32.
2. Neville BW, Damm DD, Allen CM, et. al. Erythema multiforme. In: *Oral and Maxillofacial Pathology*, 2nd ed. Philadelphia: W.B. Saunders; 2002: 674-677.
3. Schofield JK, Tatnall FM, Leigh IM. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol.* 1993 May;128(5):542-5.
4. Greenberg MS, Glick M. Erythema multiforme. In: *Burket's Oral Medicine. Diagnosis and Treatment*, 10th ed. Hamilton, Ontario: BC Decker; 2003: 57-60.
5. Silverman S Jr, Bahl S. Oral lichen planus update: clinical characteristics, treatment responses, and malignant transformation. *Am J Dent.* 1997 Dec;10(6):259-63.
6. Neville BW, Damm DD, Allen CM, et. al. Lichen planus. In: *Oral and Maxillofacial Pathology*, 2nd ed. Philadelphia: W.B. Saunders; 2002: 680-685.
7. Burkhart NW, Burker EJ, Burkes EJ, et. al. Assessing the characteristics of patients with oral lichen planus. *J Am Dent Assoc.* 1996 May;127(5):648, 651-2, 655-6 passim. Review.
8. Greenberg MS, Glick M. Erosive Lichen Planus. In: *Burket's Oral Medicine. Diagnosis and Treatment*, 10th ed. Hamilton, Ontario: BC Decker; 2003: 74-75.
9. Porter SR, Scully C, Pedersen A. Recurrent aphthous stomatitis. *Crit Rev Oral Biol Med.* 1998;9(3):306-21. Review.
10. Rogers RS 3rd. Recurrent aphthous stomatitis: clinical characteristics and associated systemic disorders. *Semin Cutan Med Surg.* 1997 Dec;16(4):278-83. Review.
11. Edres MA, Scully C, Gelbier M. Use of proprietary agents to relieve recurrent aphthous stomatitis. *Br Dent J.* 1997 Feb 22;182(4):144-6.
12. Cotran RS, Kumar V, Collins C. Blistering (bullous) diseases. In: *Robbins Pathologic Basis of Disease*; 6th edition. Philadelphia: W.B. Saunders; 1999: 1201-1203.
13. Neville BW, Damm DD, Allen CM, et. al. Pemphigus. In: *Oral and Maxillofacial Pathology*, 2nd ed. Philadelphia: W.B. Saunders; 2002: 664-667.
14. Scully C, Challacombe SJ. Pemphigus vulgaris: update on etiopathogenesis, oral manifestations, and management. *Crit Rev Oral Biol Med.* 2002;13(5):397-408. Review.
15. Mignogna MD, Lo Muzio L, Bucci E. Clinical features of gingival pemphigus vulgaris. *J Clin Periodontol.* 2001 May;28(5):489-93.
16. Greenberg MS, Glick M. Pemphigus. In: *Burket's Oral Medicine. Diagnosis and Treatment*, 10th ed. Hamilton, Ontario: BC Decker; 2003: 57-60.
17. Hashimoto T. Recent advances in the study of the pathophysiology of pemphigus. *Arch Dermatol Res.* 2003 Apr;295 Suppl 1:S2-11. Epub 2003 Jan 09. Review.
18. Harman KE, Seed PT, Gratian MJ, et. al. The severity of cutaneous and oral pemphigus is related to desmoglein 1 and 3 antibody levels. *Br J Dermatol.* 2001 Apr;144(4):775-80.
19. Toth GG, Jonkman MF. Therapy of pemphigus. *Clin Dermatol.* 2001 Nov-Dec;19(6):761-7. Review. No abstract available.
20. Ruocco E, Aurilia A, Ruocco V. Precautions and suggestions for pemphigus patients. *Dermatology.* 2001;203(3):201-7. Review.
21. Mignogna MD, Lo Muzio L, Ruoppo E, et. al. High-dose intravenous 'pulse' methylprednisone in the treatment of severe oropharyngeal pemphigus: a pilot study. *J Oral Pathol Med.* 2002 Jul;31(6):339-44.
22. Femiano F, Gombos F, Scully C. Pemphigus vulgaris with oral involvement: evaluation of two different systemic corticosteroid therapeutic protocols. *J Eur Acad Dermatol Venereol.* 2002 Jul; 16(4):353-6.
23. Ljubojevic S, Lipozencic J, Brenner S, et. al. Pemphigus vulgaris: a review of treatment over a 19-year period. *J Eur Acad Dermatol Venereol.* 2002 Nov;16(6):599-603.

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