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## **Infection Causing Oral Ulceration**

There are many infectious organisms that can lead to oral ulceration, but for the purpose of this presentation we will only discuss a few of the organisms. Be aware that many fungal organisms can lead to oral ulceration, so should be included in ones differential diagnosis when dealing with an immunocompromised patient.

### **Herpes Simplex Virus**

Herpes Simplex Virus is a DNA virus that is part of the Herpesviridae family. HSV-1 is considered the most common subtype when discussing infection of the oral cavity, but HSV-2 has been known to cause oral infection as well. The virus is transmitted by direct contact with body fluid. The average incubation time is about 7 days, but can be anywhere from 1-26 days. Once the primary infection has resolved, the virus migrates along the periaxonal sheath of the trigeminal nerve to the trigeminal ganglion. This is where it lies dormant until it is reactivated

The primary infection caused by HSV in the oral cavity is termed herpetic gingivostomatitis. It presents with multiple small vesicles involving many oral cavity sites. The vesicles rupture in 24 hours leaving ulcerations. As this process occurs, new crops of vesicles continue to appear and ulcerate. The ulcerations typically heal over a 7-14 day course. Accompanying the vesicles, one can also experience fever, arthralgia, malaise, headache, and cervical lymphadenopathy. Of note, the greatest infectivity rate occurs when the vesicles rupture. This rate decreases as the ulcers crust over.

The secondary infection is termed reactivation. This occurs in roughly 16-45% of patients who actually have the virus. Triggers to reactivation include UV light, stress, infection, and immunosuppression. One typically sees a crop of vesicles erupt on the mucocutaneous

junction of the lips, hard palate, and other attached gingiva. Prior to the appearance of the vesicles, patients may complain of a prodrome of tingling, itching, or burning. The disease usually runs its course in 7-14 days.

For the diagnosis of HSV it is recommended that fluid be obtained from an unruptured vesicle for analysis as this fluid is more likely to obtain the virus. There is a much lower yield if attempting to obtain specimens from a crusted lesion. From the fluid, most labs will use PCR to identify the virus as it tends to be faster than cultures. However, cultures can also be sent. Serologic testing is another method for diagnosis HSV. This typically involves the use of ELISA or Western blot. Western blot is very accurate, but time consuming.

The treatment of HSV related infection begins with supportive care; antipyretics, analgesics, and hydration. Valacyclovir, Famciclovir, and Acyclovir are drugs typically used to combat HSV. They work by inhibiting viral DNA polymerase. This helps to suppress and control symptoms, but does not cure the infection. Valacyclovir and Famciclovir have become more popular due to a better bioavailability than Acyclovir. If the health care provider can catch the disease in the prodrome state, topical 5% acyclovir cream for 1 week has shown to shorten the course or completely abort reactivation altogether.

## **Varicella Zoster**

The Varicella Zoster virus is also part of the Herpesviridae family. Its primary infection is termed chicken pox while its secondary infection is shingles. This virus is typically spread by respiratory droplets and less commonly by direct contact. The incubation time is roughly 2 weeks.

Following incubation, the patient develops a fever, headaches, malaise, and a rash. The vesicles associated with the rash turn to pustules that then rupture leaving ulcerations. These ulcerations then scab over. In the oral cavity, the lesions tend to involve the buccal mucosa and hard palate and have been described as having the appearance of an aphthous ulcer.

Typically, all that is needed for the diagnosis is the clinical picture. However, one may utilize direct fluorescent antibody testing on a smear obtained from a lesion. This method is rapid and highly sensitive and specific. ELISA and PCR are also options.

The vaccine against Varicella Zoster is the best way to prevent or lessen the severity of the infection. If an infection does occur, treatment is aimed at supportive care. If a severe form of the disease occurs, treatment with Valacyclovir or Acyclovir is indicated. One must be sure to monitor for secondary bacterial infections.

Shingles is considered the secondary form of Varicella Zoster. The disease presents first with a prodrome of burning or pain over a dermatome; most often V3. Following this, a maculopapular rash develops over that dermatome. Vesicles soon follow, that then turn to pustules. These pustules rupture forming ulcerations that then crust over. If there is going to be oral involvement, it is more likely going to occur after skin involvement. As with the primary infection, Shingles can usually be diagnosed with the clinical picture. If more testing is required, the modalities utilized are the same as those used for the primary infection. All that is typically

required for the treatment of Shingles is supportive care. The severe forms can be treated with Valacyclovir or Acyclovir.

## **Candidiasis**

Candidiasis is the name given to the fungal infection caused by any of the *Candida* species. These organisms are part of the normal oral flora in 40-65% of patients. Infections are noted to occur when a patient is in an immunocompromised state, suffers oral trauma, or has recently used antibiotics. Three forms of candidiasis are pseudomembranous candidiasis (thrush), atrophic candidiasis, and mucocutaneous candidiasis.

Thrush is the most common form of candidiasis encountered. It appears as a whitish plaque that can be scrapped off to reveal a “beefy” red base or ulceration that is tender to palpation. Acute atrophic candidiasis typically appears as an erythematous patch on the lateral aspect of the tongue. This form usually occurs after antibiotic use, and may precede thrush. There are two subtypes of atrophic candidiasis, chronic atrophic candidiasis and angular cheilitis. In both forms, poor denture use is a common finding. Poor fitting dentures not only can lead to tissue damage and breakdown of the tissue it is in direct contact with, but can also cause saliva to pool in the oral commissures. This leads to tissue irritation and opportunistic infection. Mucocutaneous candidiasis is the most severe form of infection caused by the *Candida* species. Patients are usually very ill prior to presenting with this form. The key to this disease is its diffuse involvement; oral cavity, lips, skin, other mucosal surfaces. The oral cavity involvement reveals lesions typical of pseudomembranous candidiasis, but more diffuse. A familial form of this disease exists. It is termed Chronic Mucocutaneous Candidiasis. It is an autosomal recessive disease in which cell-mediated immunity is impaired leaving patients more susceptible to infection.

The diagnosis of candidiasis starts with the clinical picture. Along with this, microscopic examination utilizing a KOH prep of scrapings obtained from a lesion will reveal pseudohyphae, hyphae, and yeast all present on the same slide. A culture or serum (1,3) $\beta$ -D-glucan detection assay can also be utilized if the diagnosis is unclear.

In mild, acute forms of the disease all that is usually needed for treatment is topical Nystatin. If the disease is mild, but chronic the addition of Clotrimazole troches to the topical Nystatin has shown improvement. If however, the disease is refractory or the patient is immunocompromised WITHOUT signs of systemic involvement one should consider adding oral Fluconazole. For severe, systemic forms Amphotericin B with or without Fluconazole is the treatment of choice.

## **Actinomycosis**

Actinomyces are a group of anaerobic, gram positive rods. They are typically found in the oral flora, and are considered opportunistic. Patients who suffer from this disease usually are immunocompromised or have a history of trauma or poor oral hygiene. It is an uncommon disease affecting roughly 1 in 300,000 people. Most often, patients present with a palpable neck mass. Overlying this neck mass is a purplish discoloration. Sinus tracts as well as granulomatous, suppurative lesions of the larynx, GI tract, or lungs have been reported. The

diagnosis is made through microscopic examination showing sulfur granules and gram positive, branching, filamentous rods. Culture usually takes 1-2 weeks. Treatment of the disease is aimed at surgical debridement and antibiotics. The recommended dosing is IV PCN G for 2-6 weeks followed by oral PCN for 3-6 months.

## **Autoimmune Causes of Oral Ulceration**

There are a number of autoimmune diseases that can lead to oral ulceration. Many of these have similar findings on exam, and so a more complete history and physical along with laboratory testing is needed to make a diagnosis. Be aware that infection can be overlying the true cause of the illness.

### **Lupus Erythematosus**

Lupus Erythematosus (LE) is an autoimmune (AI) disease with an incidence of roughly 40-50 per 100,000 people. It can be broken into two main types, Discoid LE, and Systemic LE. Discoid LE is a disease involving the skin and oral cavity without visceral involvement. Systemic LE involves the skin, oral cavity, and visceral organs. Oral involvement is seen more often in Systemic LE; 40% of cases vs. 25% of cases seen in Discoid LE.

The oral disease presents as erythematous plaques or erosions that can evolve into ulcerations. These lesions have a white keratotic striae radiating from the margins, and involve the buccal mucosa, gingiva, labial mucosa, and vermillion border. Other findings associated with LE are the malar rash, discoid rash, photosensitivity, arthritis, seizures, and glomerulonephritis.

Diagnosis takes into account many factors that include the clinical appearance, immunofluorescence testing of antibody-antigen complex, and the presence of ANA and anti-dsDNA antibody. The treatment of the oral manifestations is aimed at good oral hygiene along with topical steroids. If the disease is severe, systemic modalities such as steroids with or without cytotoxic agents (Cyclophosphamide and Azathioprine) are needed. Methotrexate can be used if the disease is resistant to steroids.

### **Pemphigoid**

Pemphigoid is actually a broader name given to a group of rare diseases. The incidence of these diseases is reported to affect less than 200,000 people in the United States. Three diseases that fall under the category of pemphigoid are bullous pemphigoid, cicatricial pemphigoid, and pemphigus vulgaris.

Bullous pemphigoid is caused by antibodies directed at the epithelial basement membrane eliciting an inflammatory response. The lesions in this disease appear as vesicles that can then rupture to form open ulcerations. Oral involvement is seen in 40% of cases, but typically follows skin involvement. The disease is self-limiting, but often recurs. The diagnosis is made by examining biopsy specimens with immunofluorescence. This shows deposits of IgG and C<sub>3</sub> in a linear fashion along the epithelial basement membrane. Treatment requires systemic steroids with or without cytotoxic agents. Topical steroids are used to help improve lesions.

When the patient shows resistance to treatment, the use of IV immunoglobulin should be considered. Cicatricial pemphigoid can be discussed in relation to bullous pemphigoid since the mechanism of injury is the same. The major difference between the two comes with oral involvement. Cicatricial pemphigoid has oral involvement in 85% of cases, and may be the only presentation of the disease.

Pemphigus vulgaris is caused by antibodies directed at intercellular bridges. This leads to separation of the cells in the epithelial layer resulting in very thin walled bullae. The lesions seen in this disease appear as ulcerations with a grey membranous covering. They arise in the oral cavity first, and then appear on the skin, in contrast to bullous pemphigoid. When the mucosa around a lesion is scraped, it likely will exhibit sloughing. This is the Nikolsky sign. Diagnosis of pemphigus vulgaris is made by microscopic examination of biopsy specimens. These specimens show a “tombstone” appearance along with Tzanck cells (free squamous cells forming a spherical shape). Direct immunofluorescence will show IgG against cell-cell adhesion junctions. The treatment of this disease requires the use of high dose systemic steroids along with cytotoxic agents. Plasmapheresis has also been utilized with good results. The prognosis of this disease is typically poor. Untreated, pemphigus vulgaris will result in death in 2-5 years. However, with treatment, 10-15% of patients will die due to complications arising from long-term immunosuppression.

## **Erythema Multiforme**

The etiology of erythema multiforme (EM) is unclear. However, it is thought to be the result of a hypersensitivity reaction to an infectious agent or drug exposure. The incidence is reported as affecting anywhere from 0.1-1% of the population. There are three major types; erythema multiforme minor, erythema multiforme major/Steven-Johnson syndrome, and toxic epidermal necrolysis.

Erythema multiforme minor is the most common type. It is typically the result of a pathogen exposure (HSV and Mycoplasma species). In nearly 50% of cases, the disease will begin with a flu-like illness 1-14 days prior to development of a rash. The rash that follows appears as “target lesions” on the trunk and/or palms of hands and soles of feet. In 25% of cases, ulcerations of the oral cavity occur. Overall, less than 10% of the total body surface is involved. The disease is self-limiting, and typically resolves in 2-4 weeks. The diagnosis is purely clinical while treatment is mainly supportive as the disease is self-limiting. Topical or systemic steroids can be considered if lesions are symptomatic. In addition, topical and/or oral antibiotics should be given to prevent secondary bacterial infection.

Steven-Johnson Syndrome is the diagnosis when greater than 10%, but less than 30% of the total body surface is involved with lesions. The lesions tend to involve more mucosal surfaces, and are described as being more painful. Oral involvement with hemorrhagic, ulcerative lesions is common. This form of EM is more fatal due to the greater body surface involvement leading to greater loss of fluid and secondary bacterial infections.

Toxic epidermal necrolysis is the worst form of EM. Its lesions involve greater than 30% of the total body surface. Nearly 80% of cases are related to a drug exposure. This disease

results in full thickness detachment of epidermis leading to near total or total necrosis. The most common mucosal surface involved is the oral cavity.

The diagnosis of Steven-Johnson syndrome and toxic epidermal necrolysis is made by clinical observation. Treatment involves systemic steroids, topical and systemic antibiotics, fluid and electrolyte replacement, and close monitoring in an ICU setting. The more severe forms of EM have been known to compromise a patient's airway.

### **Lichen Planus**

Lichen Planus is a T-cell mediated disease where T-cells destroy the basal cell layer of the epidermis. It is seen with an increased incidence in patients with Hepatitis C. The cutaneous lesions typically appear on flexor surfaces, and can be described by the 5 P's; purple, pruritic, planar, polygonal, papules. Roughly 70% of cases have oral involvement. The appearance of the oral lesion depends on the subtype of disease. The reticular form is characterized by the appearance of white striae on the buccal mucosa that does not scrape off. This is the most common form. The plaque form has lesions that resemble leukoplakia. They are typically located on the dorsum of tongue or buccal mucosa. The bullous form is rare, but the lesions appear as bullae that rupture leaving areas of ulceration. Finally, the erosive form has painful, erythematous erosions.

The lesions in lichen planus have to be monitored closely as malignancy is reported to arise from them in 1-5% of cases. The cutaneous lesions typically resolve in 6 months, but oral lesions tend to last longer, with reports of some lasting as long as 5 years. The diagnosis is obtained by examining the clinical picture in combination with biopsying the lesions. Treatment of oral lesions consists of topical steroids and Cyclosporine mouth wash. For severe disease, systemic steroids are needed.

### **Behcet's Syndrome**

Behcet's Syndrome is a vasculitis believed to be secondary to a hypersensitivity reaction to HSV and/or Streptococcal antigen. It is rare in the United States with an incidence of 5/100,000 population. However, it is more common in Asian/Middle Eastern countries where the incidence is reported as 1/10,000 population. The disease is nearly always seen in males, with a 16-24:1 male to female ratio. Oral ulcerations are common, and are very similar to aphthous ulcers in appearance. Other symptoms seen in the disease are recurrent genital lesions, eye lesions (uveitis, retinal vasculitis), skin lesions (erythema nodosum), polyarthritis, and meningioencephalitis. The diagnosis is based solely on the clinical appearance. Typically, topical and systemic steroids are needed to improve lesions. Systemic steroids have been shown to improve acute symptoms, but do not slow the progression or prevent recurrence of the disease.

### **Kawasaki Disease**

Kawasaki disease is a vasculitis of small and medium sized arteries affecting children. The peak age of involvement is 18-24 months with 80% of cases occurring in children less than 5 years of age. The Incidence is 67 per 100,000 children less than 5 years of age. The disease begins with a high grade fever that persists for more than 5 days. Without this, a diagnosis

cannot be made. Soon after the fever onset, oral involvement occurs. This takes the form of fissuring of the lips, oral ulcerations, and a strawberry tongue. Three to five days after fever onset, an erythematous, maculopapular rash appears. It starts on the palms of hands and soles of feet and soon spreads to the trunk. Other symptoms include dry conjunctivitis, desquamation of the skin, cervical adenopathy, and coronary aneurysms. The coronary aneurysms typically appear 2-8 weeks after the main symptoms. The diagnosis is made based on clinical presentation. However, echocardiography should be performed 7 days after the disease onset, and then 6-8 weeks later to determine if coronary aneurysms have developed.

Treatment of Kawasaki disease includes the use of Aspirin, IV immunoglobulin, and bed rest. Aspirin is used at high doses initially for its anti-inflammatory action. Later, however, it is used at a lower dose for its antiplatelet effect. If not treated, 25% of patients will develop coronary aneurysms. Compare this to only 1-10% of cases developing coronary aneurysms if treatment is started early. One can expect coronary aneurysms to resolve over a 2 year period.

## **Aphthous Ulcers**

Although the etiology of aphthous ulcers is not clear, it is believed the immune system plays a role in their development. They are considered the most common cause of non-traumatic ulcerations of the oral cavity with roughly 10-20% of the population having experienced them. Three classifications exist. They are minor, major, and herpetiform ulcers.

Minor aphthous ulcers are less than 1 cm in diameter and located typically on freely mobile oral mucosa. They appear as a well-delineated white lesion with an erythematous halo. Prior to appearance, some patients report a prodrome of burning or tingling in the area of involvement. These ulcers tend to resolve in 7-10 days and almost never scar.

Major aphthous ulcers are larger than 1 cm. They can be found on freely mobile oral mucosa, the tongue, and palate. These ulcers tend to last much longer with reports of some lasting 6 or more weeks. Unlike the minor form, however, these more often scar upon healing.

Herpetiform ulcers appear as a small, 1-3mm in diameter ulceration arising in crops of 20-200 ulcers. They are located on freely mobile oral mucosa, the tongue, and palate. They tend to last 1-2 weeks, and are extremely painful. They are called herpetiform because the ulcerations resemble those of HSV, but there is no vesicular phase as there is in HSV lesions.

The treatment of aphthous ulcers begins with topical preparations. Topical Tetracycline solution for 5-7 days has shown good results while topical steroids have been shown to shorten disease duration. Sucralfate suspension has shown to improve pain as well as shorten the disease duration. Major aphthous ulcers or more severe forms of disease tend to require systemic steroids.

## **Radiation/Chemotherapy Induced Mucositis**

Treatment options for head and neck cancer include the use of radiation and chemotherapy. However, one potential side effect from using these treatment modalities is the development of mucositis, the inflammation of mucus membranes. The incidence of

radiation/chemotherapy induced mucositis is reported to be around 30-40% of patients receiving chemotherapy or radiation. Chemotherapy induced mucositis typically occurs within 5-10 days of starting therapy while radiation induced mucositis is seen during the 2<sup>nd</sup> week of therapy.

There are 5 phases to the overall process. First, is the initiation phase. During this phase free radicals develop in response to therapy leading to the initial damage. Second, message generation occurs. During this phase transcription factors are activated. These attract inflammatory activators IL-1 and TNF- $\alpha$ . These inflammatory activators cause increased inflammation, dilated vessels and further tissue damage in a phase termed the amplification phase. The next phase is termed the ulceration phase. Ulceration develops as a result of immune mediated tissue damage and microtrauma from speech, swallowing, and mastication. In addition to this, secondary bacterial infections occur leading to further tissue damage. The last phase is the healing phase. During this phase, ulcers re-epithelialize and bacteria are destroyed. The typical disease course runs 2-3 weeks for both chemotherapy and radiation induced mucositis.

Treatment of mucositis is aimed at four areas. First, good oral hygiene must be maintained. Patients should rinse with dilute hydrogen peroxide or sodium bicarbonate solutions. Also the use of soft tooth brushes and sponge-tipped applicators for removing plaques/crusting is needed. The second goal of treatment is to prevent or eradicate infection. This is done through the use of fluoride rinses and antifungal agents. The third goal is to maintain good moisture. This can be achieved through the use of petroleum jelly and mineral oil. The last goal of therapy is pain control. The use of topical Lidocaine, Sulcralfate, and systemic pain medications can all help to accomplish this goal.

## **Premalignancy/Malignancy – Presentation**

An area that cannot be overlooked when discussing oral ulceration is malignancy. For the purpose of this discussion only basic information will be given about this topic. The main piece of information to take away from this section is that any ulceration that fails to heal in 1-2 weeks should be biopsied.

Before we can discuss malignant lesions, we need to examine some premalignant lesions. The first is leukoplakia. It appears as a whitish plaque that cannot be scrapped off. The incidence of malignancy arising from these lesions is anywhere from 5-20%, so close monitoring is necessary. Microscopic examination of biopsies will reveal hyperkeratosis and atypia. One should also note that lesions involving the lateral tongue, lower lip, and floor of mouth are more likely to progress to malignancy. Another premalignant lesion is erythroplakia. This serious lesion appears as a red patch or macule with a soft, velvety texture. It requires close observation as malignant potential is extremely high. Roughly 60-90% of untreated cases will undergo malignant transformation. Treatment is usually surgical excision or laser ablation.

Oral cavity cancers account for roughly 30% of all head and neck cancer making it the most common site of head and neck cancer. The symptoms/findings involved with oral malignancy include non-healing ulcerations, pain, expansile lesions, trismus, dysphagia, odonyphagia, halitosis, numbness in lower teeth (inferior alveolar nerve involvement), and others. Indicators of more aggressive tumors are those tumors greater than 1 cm in size, invading 4 mm or more, or exhibiting perineural, lymphatic, or vascular invasion.

Squamous cell carcinoma is most common type of cancer found in the oral cavity, accounting for nearly 90% of all cases. A less aggressive variant of squamous cell carcinoma is verrucous carcinoma. It is typically located on the buccal mucosa, and appears as a warty lesion. It is rare that this type of cancer ever metastasizes or exhibits deep invasion. Basal cell carcinoma can also be found in the oral cavity, but more commonly involves the upper lip. Salivary gland malignancies also appear in the oral cavity with adenoid cystic carcinoma being the most common. Other malignancies involving the oral cavity include lymphoma, sarcomas (rhabdomyosarcoma and liposarcoma most commonly), and melanoma.

## **Necrotizing Sialometaplasia**

Necrotizing sialometaplasia is a lesion that needs to be discussed as it is commonly mistaken for squamous cell carcinoma. It is a non-neoplastic, inflammatory lesion of salivary glands thought to be the result of vascular ischemia. It is typically located on the hard palate, but can be just about anywhere in the oral cavity. It presents as a 1-3cm ulceration, and may exhibit bony erosion. Spontaneous resolution occurs within 5 weeks, but can take up to 9 weeks. Diagnosis can only be made by a good incisional biopsy. If there is any question about the diagnosis after biopsy, get another biopsy. Treatment is only supportive as these lesions resolve on their own.

## **Burning Mouth Syndrome**

Burning mouth syndrome is included in this talk because many of the causes of oral ulceration can present initially with this syndrome's clinical picture. The main symptoms seen are intense oral pain described as burning or scalding, altered taste, and xerostomia. Other symptoms reported are painful mastication, jaw clenching, multiple mood and emotional disturbances (anxiety, irritability, depression). The pain associated is constant throughout the day, and lasts for months at a time. There are two main types, primary and secondary burning mouth syndrome. These are separated on the basis of whether a cause can be found. Primary is idiopathic while secondary has an identifiable cause.

It is good to note that this syndrome is seen more often in perimenopausal and postmenopausal women. A theory exists that the lack of estrogen in women who are peri- or postmenopausal leads to atrophy of the oral mucosa. This in turn leads to altered nerve function as well as allowing for increased inflammation. Some other known and proposed causes include immunologic reactions to allergens (peanuts, benzoyl peroxide), nutritional deficiency (B vitamins, folate, iron), infectious agents (*Candida* species), iatrogenic causes (radiation and chemotherapy), and neurologic disorders (anxiety, depression, Diabetic neuropathy).

The prognosis isn't great for patients suffering from burning mouth syndrome as only 3% of patients with the primary type will have full resolution. However, 50-60% of patients will improve. Treatment depends on the type. For the primary type, many different treatment modalities have been attempted, but nothing is agreed upon as the main treatment. Treatments that have shown some improvement include SSRIs, benzodiazepines, TCAs, psychotherapy, oral Lidocaine, neuropathic analgesics, and systemic pain medications. The treatment of secondary burning mouth syndrome is aimed at treating the underlying cause.

## **Conclusion**

In conclusion, there are many causes of oral ulcerations, and this discussion only mentioned a few of them. Many of the clinical findings overlap between the different disease states, thus attention to detail is important (good history and physical) to arrive at a diagnosis. It is very important to make a definitive diagnosis as treatment can vary drastically; Necrotizing sialometaplasia vs. invasive squamous cell carcinoma of the hard palate. Remember, if an ulceration has not healed in 1-2 weeks, biopsy it.

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