Herpes Simplex Virus–Related Oral Mucositis in Patients With Lymphoma

Maria D. Guerrero, RN, ANP-C, AOCNP®, and Karen K. Swenson, RN, PhD, AOCN®

A 58-year-old man named J.S. was diagnosed with non-Hodgkin lymphoma and underwent treatment with standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy. He presented to his local outpatient clinic for evaluation and laboratory tests on day 10 after cycle 3. During this visit, J.S. reported great difficulty opening his mouth with significant gingival and lingual pain when eating and drinking in spite of prophylactic oral care. Laboratory test results revealed a white blood cell count of 0.9 k/ul, hemoglobin level of 8.9 g/dl, platelets of 100 k/ul, serum creatinine level of 1 mg/dl, and blood urea nitrogen level of 29 mg/dl.

Examination revealed a man in good physical shape with normal vital signs and oxygen saturation level on room air. Although his oral mucosa was pink, his tongue and buccal mucosa had bilateral ulcerations with xerostomia (dry mouth). Upper and lower gingivae were intact but sensitive to touch. The remainder of his physical examination was normal. He was provided with education on continuing oral care, antivirals, analgesics, and neutropenic precautions. He did receive growth factor support 24 hours after completion of therapy. Diagnosis based on clinical presentation was herpes simplex virus (HSV)-related oral mucositis.

Oral Mucositis

Studies have investigated the incidence and management of oral mucositis as well as its significant consequences, which may occur as a complication of mucositis. However, limited information exists on the incidence of oral mucositis resulting from a viral etiology such as HSV (Chen et al., 2011). No clear evidence supports routine cultures or empiric treatment with antivirals for presumed HSV-related oral mucositis. Healthcare professionals must identify, assess, and manage oral mucositis and should be aware that HSV infection is a potential cause or complication of oral mucositis.

Oral mucositis is an inflammatory process in the oral mucosa often caused by chemotherapy agents or radiotherapy. Oral mucositis is characterized by clinical signs and symptoms observed in the oral cavity. In the general oncology population, oral mucositis ranges from mild sensations in the oral cavity to a myriad of confluent ulcerative lesions. Mucositis can affect the continuum of mucosa, including the oral and gastrointestinal mucosa, from the mouth to the anus (Eilers & Million, 2007). For purposes of this case study, the authors will focus on the oral cavity.

Incidence

Oral mucositis occurs frequently in the general oncology population. Sonis (2004) described a five-stage model of evidence-based pathogenesis of mucositis (see Table 1). Inflammatory cells and pro-inflammatory cytokines, including cyclo-oxygenase-2, nuclear factor-kappa B, tumor necrosis factor-alpha, and interleukin-6, are upregulated in oral mucositis (Lalla et al., 2008). The identification of these pathways paves the way for understanding the pathogenesis of oral mucositis and provides potential therapeutic targets for the development of new therapies.

Pathophysiology

Oral mucositis was previously considered a simple process because of the non-specific damage to epithelial cells by cytotoxic therapies and delayed replacement of these cells in the basal layer, resulting in ulceration on the mucosal surfaces (Sonis, 2004). However, healthcare professionals now know that the pathogenesis of mucositis is multifactorial and more complex than simply epithelial damage (Lalla et al., 2008). Sonis (2004) reported that 51% of patients receiving standard chemotherapy for lymphoma develop oral and/or gastrointestinal mucositis. The degree, extent, and site of oral mucositis that develops in any particular patient may depend on factors such as age, underlying systemic disease, and race, as well as tissue-specific factors (e.g., epithelial types, local microbial environment, function). In addition, conflicting evidence exists for the influence of gender on risk for mucositis, with some studies reporting increased risk for mucositis in females and others finding no gender effect (Lalla, Sonis, & Peterson, 2008). Smoking, obesity, cachexia, history of prior chemotherapy, and poor oral hygiene and dentition also place patients at increased risk of oral mucositis (Eilers & Million, 2007). Genetics also may play a role in mucositis development (Cawley & Benson, 2005).
Tissue injury caused by chemotherapy-induced cellular damage. Epithelial proliferation as well as cellular and tissue differentiation, restoring the integrity of the epithelium. Note. Based on information from Cawley & Benson, 2004; Sonis, 2004.

HSV-1 and HSV-2 belong to the family Herpesviridae and are virtually identical, sharing about 50% of their DNA. Both types infect the mucosal surfaces of the body: HSV-1 most often in the mouth because of an affinity for the trigeminal ganglia and HSV-2 in the genitals with affinity for the lumbosacral ganglia. Both establish latency in the nervous system and about 80% of immunocompetent hosts who are infected have no noticeable symptoms (Salvaggio, Lutwick, Seenivasan, & Kumar, 2012). These viruses can be spread from viral shedding when no symptoms are present.

The virus can be reactivated by various stimuli, such as fever, trauma, emotional stress, or immunosuppression from chemotherapy which result in overt or covert recurrence of the initial infection and shedding of HSV. A patient who is immunocompromised also is at equal risk of acquiring HSV-1 and HSV-2 both orally and genitally. Reactivation is more common than a primary infection (Fitzmorris, Greene, Sandin, & Field, 2000).

Mode of Transmission

HSV-1 and HSV-2 are transmitted by mucosal or cutaneous/mucosal contact, and infection occurs via inoculation of the virus into susceptible mucosal surfaces or through small cracks in the skin. HSV-2 is primarily transmitted via sexual contact in immunocompetent individuals. These viruses are readily inactivated at room temperature and by drying; therefore, aerosol spread is rare (Salvaggio et al., 2012).

Assessment of Oral Mucosa

Educating staff is important to create awareness of the risk factors, clinical presentation, diagnostic tests, and assessment tools to develop a management plan. Oral assessment is an ongoing process, and its findings are essential to developing a management plan that will be implemented and evaluated on an ongoing basis (Eilers & Million, 2007). Initial assessment establishes a baseline of the oral cavity before the start of therapy. The lips, tongue, gingivae, and other surfaces should be evaluated, along with palpation of visible lesions and evaluation of the patient's ability to swallow and speak. Proper lighting is essential to visually inspect the oral cavity for any abnormalities and establish a description for what is normal for each patient. Several clinical assessment tools are available for assessment and documentation of the oral mucosa. These tools provide grading systems for the collection of subjective and objective data (Eilers & Epstein, 2004). Common tools include the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 3.0; the Oral Mucositis Assessment Scale; and the

<table>
<thead>
<tr>
<th>Table 1. Pathophysiology of Oral Mucositis</th>
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<td>Stage</td>
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<td>------------------------</td>
</tr>
<tr>
<td>I. Initiation</td>
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<tr>
<td>II. Upregulation and message generation</td>
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<tr>
<td>III. Signaling and amplification</td>
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<tr>
<td>IV. Ulceration</td>
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<td>V. Healing</td>
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Note. Based on information from Cawley & Benson, 2004; Sonis, 2004.
Patients who have a prior history of an HSV infection, are seropositive for HSV, and are immunocompromised have an increased risk of HSV-related oral mucositis. Patients need to understand the risk of oral mucositis, the importance of reporting early symptoms, and how to adhere to oral care regimens. HSV-related oral mucositis should be suspected if extreme pain, vesicular lesions, or a prolonged course of mucositis are present (Negrin, Bedard, & Toljanic, 2014).

Differential diagnosis also should be considered when assessing patients with signs and symptoms of oral mucositis. These include poor hygiene; infection (e.g., *Candidiasis*, HSV); aphthous ulcers (canker sore); trauma to mucosa; and Reiter syndrome conjunctivitis, urethritis, and arthritis with oral, genital, or mucocutaneous lesions (Camp-Sorrell & Hawkins, 2006).

### Diagnostic Tests

The gold standard diagnostic test for HSV-related oral mucositis is isolation of HSV tissue culture (results usually take two to seven days). A more rapid diagnostic test for mucocutaneous lesions uses staining of skin scrapings. Polymerase chain reaction is a diagnostic test used for the rapid and accurate diagnosis of cerebral spinal fluid infection with HSV (encephalitis); however, this test also can be used to confirm infection in the oral cavity (Brady & Bernstein, 2004).

### Treatment

The management of oral mucositis to date has typically been symptom control. The Mucositis Study Group of the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) developed clinical practice guidelines for the management of mucositis (Lalla et al., 2008). The guidelines are subdivided into separate sections that focus on nutritional support, pain control, oral decontamination, palliation of dry mouth, management of oral bleeding, and therapeutic interventions for oral mucositis. Table 2 lists management of HSV-related oral mucositis and incorporates MASCC/ISOO guidelines with therapeutic interventions for HSV.

For immunocompetent patients with either oral or genital HSV, treatment with acyclovir or valacyclovir for 7–10 days is recommended (Brady & Bernstein, 2004). Treatment also can be episodic and used at the first sign or symptom of outbreak for 1–5 days to decrease the symptoms of HSV infection, or administered prophylactically to prevent recurrences. Suppressive therapy decreases asymptomatic shedding, reduces transmission of HSV, and enhances healing and pain relief (Brady & Bernstein, 2004).

Immunocompromised patients, such as J.S. in the case study, require timely identification and initiation of antiviral therapy. Therapy can certainly commence prior to report of a positive culture. HSV infection can become disseminated and progress to encephalitis and lesions can develop secondary fungal or bacterial infections. Therapy often includes IV infusion of acyclovir until clinical and hematologic resolution. Clinicians should ensure that pain control and fluid and nutritional support are provided (Negrin et al., 2014).

### Table 2. Management of HSV–Related Oral Mucositis

<table>
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<th>Variable</th>
<th>Recommendations</th>
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<tr>
<td>Pain control</td>
<td>• Use saline mouth rinses, ice chips, topical mouth rinses and lidocaine or lidocaine alone, and topical mucosal bioadherent agents (no top-level evidence) to relieve pain. • Systemic analgesics may be used if not relieved by nonpharmacologic measures, topical anesthetics, or bioadherent agents.</td>
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<tr>
<td>Oral hygiene or decontamination to prevent secondary infection of oral lesions</td>
<td>• Brush with a soft toothbrush and use floss. • Use nonmedicated rinses (e.g., saline or sodium bicarbonate rinses). • Avoid sucralfate, glutamine, and chlorhexidine, as well as alcohol-based rinses. • Antimicrobial washes are not recommended for prevention.</td>
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<td>Nutritional support</td>
<td>• Consult with registered dietitian. • Encourage a soft diet high in calories and protein. • Promote dietary supplements. • Encourage hyperalimentation; if necessary, use PEG as clinically indicated.</td>
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<td>Therapeutic interventions</td>
<td>• Culture lesions to rule out HSV infection. • HSV prophylaxis in patients receiving high-dose chemotherapy and in those who are positive for HSV and receiving immunosuppressive therapy or HSCT. • Prophylaxis includes acyclovir 200–400 mg two to five times daily or 5 mg/kg via IV every eight hours. • Treat active infections with parenteral acyclovir or, if tolerated, oral acyclovir or valacyclovir. • Treat secondary infections (e.g., <em>Candidiasis</em>).</td>
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**Note:** Based on information from Fitzmorris et al., 2000; Lalla et al., 2008; Negrin et al., 2014; Treister, 2013.

**Conclusion**

Oral mucositis is a common complication in patients with lymphoma receiving chemotherapy. However, oral mucositis is not always related to chemotherapy; HSV-related oral mucositis should be considered as part of the differential diagnosis. Nurses play an important role in early identification and appropriate management of the patient.

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**Key words:** herpes simplex virus; oral mucositis; lymphoma; immunocompromised patients

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**Endnotes:**

- HSCT—hematopoietic stem cell transplantation; HSV—herpes simplex virus; PEG—percutaneous endoscopic gastrostomy

**References:**

Lalla et al., 2008.
Negrin et al., 2014.
Treister, 2013.
References


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