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Atypical herpetic ulcerations in COVID-19 positive patients: A report of three cases

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Since the global COVID-19 pandemic, numerous reports have been made regarding oral lesions seen in COVID-19 patients. It remains unclear whether or not these are true manifestations of COVID-19. Here we present 3 patients who were hospitalized for COVID-19 and who developed atypical herpetic ulcerations during their treatment with remdesivir (Veklury) and steroids. In healthy patients, recurrent infection by herpes simplex virus (HSV) presents as lesions only on the lips and the attached oral mucosa. Atypical herpetic ulcerations are seen in immunocompromised patients. They present as large, stellate shaped ulcerations with raised borders and may involve movable mucosa. The 3 cases presented in this report resembled the atypical herpetic ulcerations typically seen in patients with immunosuppression. Through our report, we aimed to introduce the possibility of atypical herpetic ulcers in patients being treated for COVID-19, to allow for their timely diagnosis and to raise awareness of the underlying immunocompromised state. (Oral Surg Oral Med Oral Pathol Oral Radiol 2022;000:e1−e4)

There have been many reports of oral manifestations of COVID-19 to date. The most well-known is dysgeusia, and studies have proposed direct mechanisms of pathogenesis by the virus such as the invasion of the olfactory and gustatory nerves, angiotensin II imbalance, augmentation of proinflammatory cytokines, and disturbances in salivary glands and sialic acid.[1] Other reported manifestations include ulcers, erosions, bulla, vesicle, pustule, macule, papule, plaque, erythema, and petechiae on various sites of the oral cavity including the tongue, labial mucosa, palate, gingiva, buccal mucosa, oropharynx, and tonsils.[2,3] Other than dysgeusia, the causal relationship has not been established between the SARS-CoV-2 and these reported oral manifestations. Indeed, the nonspecificity and variability of these reported lesions suggest that they may have been caused by indirect or secondary mechanisms.

Herpes simplex virus (HSV) represents one of the most prevalent viral infections in the orofacial region. Recurrent HSV infections result from reactivation of HSV that was previously dormant in a neural ganglion in a patient with prior infection and presents with a localized cluster of lesions without systemic manifestations. In immunocompetent patients, recurrent HSV only occurs on the labial mucosa (herpes labialis) and the attached mucosa.[4]

Immunosuppressed patients have a defect in cell-mediated immunity that leads to a decline in the body's immune response to HSV that may lead to an atypical clinical oral presentation. With immunosuppression, recurrent HSV infection may be "atypical" by presenting on the movable mucosa such as the tongue, vestibules, and the buccal mucosa. In such cases, the herpetic ulcers can be significantly larger, extremely painful, and slow in healing, lasting weeks to months.[4]

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METHODS AND MATERIALS

Herein we presented 3 patients who were hospitalized for COVID-19 and who presented with atypical herpetic ulcerations. It remains unclear if treatment with high dose steroids was solely responsible for their occurrence or whether remdesivir, comorbidities, and SARS-CoV-2 infection also played a significant role.

Patient 1

Patient 1 was an 83-year-old female admitted for acute respiratory failure due to COVID-19. Her pertinent medical history included hypertension, hyperlipidemia, and hypothyroidism. On day 11 of her hospital admission, oral pathology was consulted for evaluation of oral pain with difficulty eating and drinking. Upon examination, stellate shaped ulcerations with raised yellow white borders were found on her ventral and lateral tongue (Figure 1). Pseudomembranous candidiasis was also identified. Before the oral pathology consult, her treatment consisted of a 5-day course of remdesivir (200mg once and then 100mg daily for 4 days) with a 10-day course of dexamethasone (6mg daily).

Patient 2

Patient 2 was a 70-year-old obese female who presented to the hospital with dyspnea secondary to COVID-19. Her treatment also consisted of a 5-day course of remdesivir (Veklury) (200mg once and then 100mg daily for 4 days) with a 10-day course of dexamethasone (Decadron) (6mg daily), followed by 40mg of methylprednisolone (Medrol)

A B

Fig. 1. **(A)** Stellate shaped ulcer with raised white border on the ventral surface of the tongue. **(B)** Irregular shaped ulcers with raised white borders on the lateral tongue.

for additional 12 days. On day 22, oral pathology was consulted for oral pain and ulcers. Oral examination revealed stellate shaped ulcers surrounded by raised white borders on the dorsal and lateral borders of her tongue as well as on the labial mucosa (Figure 2). Pseudomembranous candidiasis was also present.

Patient 3

Patient 3 was a 75-year-old-male with chronic obstructive pulmonary disease, coronary and peripheral artery disease, diabetes, end stage renal disease, and recent diagnosis of lung carcinoma. He was admitted to the hospital for acute hypoxic respiratory failure due to COVID-19. Like the others, his treatment consisted of a 5-day course of remdesivir (200mg once and then 100mg daily for 4 days) with a 10-day course of dexamethasone (6mg daily). Additionally, he was treated with convalescent plasma. Oral pathology was consulted on day 20, 10 days after the 10-day course of steroids was completed. Oral examination revealed ulcerations of his labial mucosa and anterior tongue (Figure 3).

A B

Fig. 2. **(A)** Ulcers on the anterior tip of the tongue. **(B)** Large ulcer on the labial mucosa. The patient also had candidiasis.

Fig 3. **(A)** Ulcer on the anterior tip of the tongue. **(B)** Ulcer on the labial mucosa.

Cytologic smears were performed on all 3 patients. Papanicolaou stained cytology revealed virally altered epithelial cells with glassy nuclei and nuclear molding consistent with HSV infection (Figure 4).

DISCUSSION

Recurrent HSV infection of the oral cavity presents differently in immunocompetent and immunocompromised patients. In immunocompetent patients, the herpetic lesions are almost always confined to the lip or the fixed mucosa (attached gingiva and hard palate) and present as small 1-3mm vesicles which eventually collapse and form ulcers.[4] In various settings of immunosuppression, such as acquired immunodeficiency syndrome (AIDS), long-term systemic corticosteroid therapy, and chemotherapy, herpes reactivation undergoes a more severe clinical presentation.[4–6] In such cases, the herpetic lesions can present atypically in the oral cavity, forming significantly larger ulcers with raised yellow-white borders, often affecting the movable mucosa.[4]

This case series presented 3 patients who were hospitalized for COVID-19 and who developed atypical herpetic ulcerations during their treatment. These herpetic ulcerations had the clinical presentation that would normally be seen in immunocompromised patients. Two of the 3 patients had undergone a 10-day course of systemic steroids, which we believed was too short of duration to cause immunosuppression by itself. This was supported by their relatively uncommon occurrence in the numerous numbers of hospitalized patients treated with steroid therapy. This led us to suspect that some other factor(s)—possibly comorbidities, remdesivir, or the virus itself—may act synergistically with the systemic steroids to cause the atypical herpetic eruptions in these patients. One of the 3 patients, however, was on systemic steroids for 22 days, in which case immunosuppression could be reasonably expected.

A literature review was performed to explore the possible explanations for the atypical presentations of HSV in our patients. Immune dysregulation induced by COVID-19 has been reported by numerous studies, but whether or not such dysregulation would significantly affect the host's defenses against other pathogens remains unclear.[7–9] Nonetheless, there are numerous

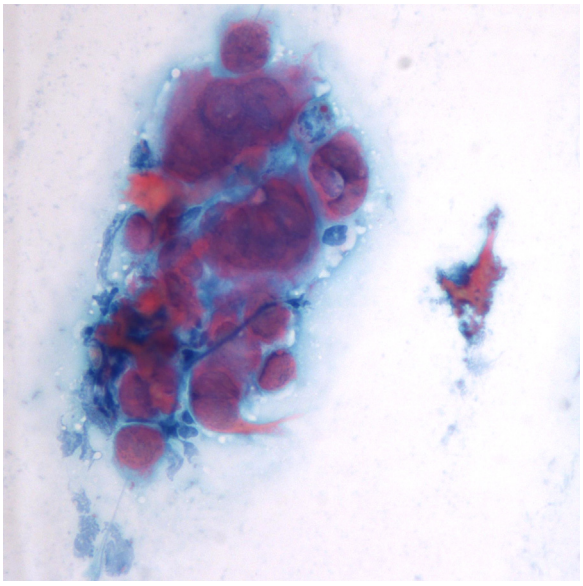

Fig. 4. Representative cytologic smear of the lower labial mucosa of patient 3. Papanicolaou stain demonstrates virally altered epithelial cells with multiple molded nuclei exhibiting ballooning degeneration.

reports of opportunistic infections (e.g., Aspergillosis, Candidiasis, HSV, CMV, etc.) in hospitalized COVID-19 patients receiving immunosuppressive therapy.[10,11] Taken together, it seems that COVID-19 patients receiving systemic steroid therapy are at an increased risk for developing opportunistic infections, indicating a compromised immune system. No evidence for the relationship between remdesivir and immunosuppression was found.

The diagnosis of atypical herpetic ulcers can often be confused with other lesions such as aphthous ulcers. Proper diagnosis is important as these atypical herpetic ulcerations can be long lasting and extremely debilitating. Cytologic smears or tissue biopsy is required for the definitive diagnosis of herpes. Saliva testing for herpes is not recommended because asymptomatic shedding of HSV has been documented and therefore the test has a significant risk of false positive results.[12]

CONCLUSION

We presented 3 COVID-19 patients who presented with atypical herpetic ulcerations. Awareness of the possible atypical presentations of herpes in COVID-19 patients undergoing systemic therapy will allow for their timely diagnosis and appropriate treatment. We believe that the steroid treatment in the setting of SARS-CoV-2 infection was responsible for reactivation of the herpes virus leading to ulcer formation.

PRESENTATION

The abstract was presented at the past meeting of Research Day at New York Presbyterian Queens Atypical Herpetic Ulcerations in COVID-19 Positive Patients: A Report of Three Cases.

DISCLOSURE

None.

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