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Case Report

Oral Chronic Graft-versus-Host Disease in Post-Hematopoietic Stem Cell Transplant Patients Following SARS-CoV-2 Vaccination: Case Reports

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Case report · Graft-versus-host disease · SARS-CoV-2 · Vaccination

Abstract
Patients receiving allogeneic hematopoietic stem cell transplant may experience graft-versus-host disease (GVHD) in which donor immune cells cause an immune reaction in host tissues. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccines are highly effective in prevention of severe coronavirus-2019 (COVID-19) disease, but the vaccine can result in immune activation and GVHD. Herein, we report 4 cases of oral manifestations that may have been stimulated by COVID-19 or vaccination with Pfizer or Moderna vaccines. We believe this study is the first to report oral changes driven by an inflammatory/immune mechanism leading to oral symptomatic cGVHD. The clinical impact of this study is early recognition and appropriate management of oral symptomatic cGVHD following COVID-19 disease or SARS-CoV-2 vaccination.

Introduction

Graft-versus-host disease (GVHD) is an immune condition that occurs in recipients of allogeneic hematopoietic stem cell transplant (HCT) when immune cells from the donor recognize host tissues and cause immune reaction [1] and can be acute or chronic. Chronic

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GVHD (cGVHD) typically appears 100 days or more after HCT with prevalence ranging from 30 to 70% depending on donor type, stem cell source, conditioning regimen, and GVHD prophylaxis [2]. The mouth is one of the most common sites of cGVHD with some reports as high as 85% [3]. Oral GVHD has been reported in approximately 70% of patients with cGVHD [4], with up to 50% steroid refractory [5]. Oral GVHD may result in mucosal lesions and related symptoms and dry mouth that impact comfort, diet and nutrition, and increased risk of infection affecting quality of life [4, 6].

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccines are highly effective in the prevention of severe coronavirus-2019 (COVID-19) disease which can be fatal if severe. However, the vaccine can trigger robust release of immunomodulatory cytokines, resulting in immune activation and possibly GVHD [7]. The incidence of adverse events following SARS-CoV-2 vaccines, new onset of cGVHD, or worsening of existing cGVHD was recently reported in 113 HCT patients who received one or both doses of mRNA vaccine post-transplant [7] Safety, efficacy, and impact upon GVHD was reviewed. Patients experienced myalgia/arthralgia and fatigue more commonly after the second dose of vaccine. Injection site pain was reported in 40.4–43.8%. Changes in liver function were seen in 18.6%; and neutropenia, thrombocytopenia, and lymphopenia in 13.3%, 11.5%, 8.8%, respectively. Of the patients who were undergoing treatment for cGVHD, worsening of GVHD was noted in 3.5% and new onset of cGVHD occurred in 9.7% of allogeneic HCT.

We are not aware of reports of oral lichenoid reactions or oral cGVHD in patients following either Pfizer (BNT162b2) or Moderna (mRNA-1273) vaccines, and present cases reflecting potential impact upon existing oral mucosal reactions or stimulation of new clinical symptoms that may be associated with COVID-19 disease or vaccination. We report 4 cases of oral manifestations that may be stimulated by COVID-19 and oral changes that developed or were aggravated following vaccination for SARS-CoV-2. We believe this study represents the first report of oral changes driven by an inflammatory/immune mechanism, leading to oral symptomatic cGVHD. Recognizing the potential to experience oral reactions following vaccination may facilitate early recognition and appropriate management.

Case Presentation

Patient 1 (post-HCT: 10 months): A 74-year-old male with primary myelofibrosis underwent HCT from matched unrelated donor in March of 2020. He did well without acute or cGVHD. He received first dose of Pfizer vaccine in January 2021 and second dose in February 2021. He had no side effect after the first vaccine shot but after the second, he developed symptoms of fatigue, nausea, diarrhea, muscle aches, and injection site pain that lasted for 7 days. Two weeks following the first dose of vaccine he developed mouth soreness with moderate to severe buccal and palatal mucosal erythema (Fig. 1). Oral changes were accompanied by macular erythematous rash. He was on gradual taper of dose of tacrolimus at that time. For new onset oral and skin cGVHD, he was started on prednisone and ruxolitinib. He was able to come off prednisone and now on tacrolimus and ruxolitinib. Although not an FDA indication, ruxolitinib is often started in first-line de novo cGVHD in severe cases or in patients with perceived poor tolerability of corticosteroids.

Patient 2 (post-HCT: 20 months): A 70-year-old male underwent HCT from an unrelated donor for secondary AML from prior myelofibrosis in June 2019. He did well post-HCT with no acute or cGVHD. He was on gradual tapering of tacrolimus since October 2020 and never had any exacerbation of GVHD. When seen in early February 2021, he had oral changes consistent with mild oral GVHD (Fig. 2a). He was advised to resume steroid rinses and halted any further taper of the tacrolimus. After a couple of weeks, he did not report any worsening of the oral

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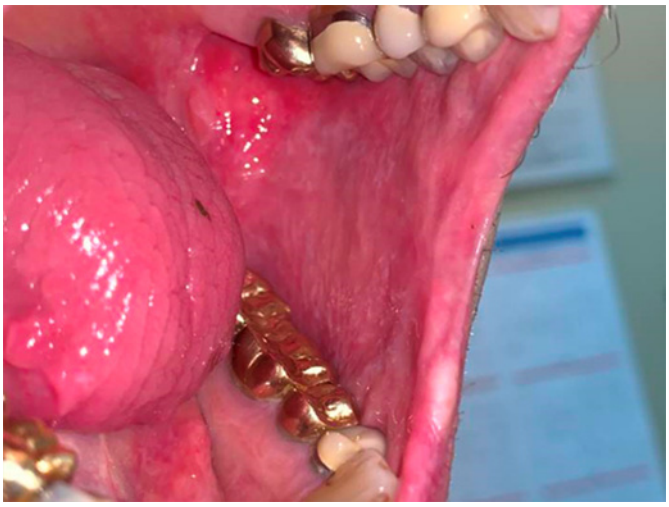

Fig. 1. Patient had primary myelofibrosis and underwent HCT from matched unrelated donor in March of 2020 with no acute or cGVHD. Patient received first dose of Pfizer vaccine in January 2021 and second dose in February 2021. Two weeks following the first dose of vaccine, he developed moderate to severe buccal and palatal mucosal erythema.

lesions. However, on March 09, 2021, he presented with oral sensitivity, and examination revealed prominent white lichenoid lesions (Fig. 2b) 1 month following the initial Moderna (mRNA-1273) vaccine on February 16, 2021. As a result, tacrolimus dosage was increased, and oral steroid rinses were continued. At his subsequent visit on March 24, 2021, oral examination showed improvement in oral GVHD (Fig. 2c).

Patient 3 (post-HCT: 26 months): A 73-year-old male received allogeneic HCT for acute lymphocytic leukemia in March 2019. He developed GVHD 1 year later with skin, liver, and oral involvement. He had symptoms of dry mouth, sensitive buccal mucosa and tongue, and reduced taste. Patient's oral sensitivity and loss of taste affected eating. In May 2020, he developed classical oral lichenoid changes with extensive striations, severe erythema on the buccal mucosa and lateral border of the tongue, soft palate and attached gingiva and ulcers on hard palatal gingiva in the molar regions. Initial oral treatment with budesonide and doxepin rinses for pain was provided. At follow-up in June 2020, he was much improved without pain and ate well. Besides dry mouth, all oral changes due to cGVHD resolved. He remained on stable doses of ibrutinib, tacrolimus, and low-dose prednisone. He received Pfizer (BNT162b2) 2 doses, 3 weeks apart in May 2021. Two weeks after the last dose, he presented with oral pain and skin rash. No other triggers were identified. When seen, exfoliative dermatitis of the hands which had followed vaccination was reported improving. Oral tissues were moist with saliva. However, extensive striae and severe erythema was present on the right buccal mucosa with plaque-like changes and striations, on the left striations, 3 mm ulceration and severe erythema and ulceration on the palatal gingiva of the upper bicuspid areas were seen. Oral symptoms had been in remission for 9 months prior to recurrence. Budesonide rinse was resumed, and patient started on ruxolitinib and extracorporeal photopheresis. Symptoms improved after 2 months of treatment.

Patient 4 (post-HCT: 206 months): A 58-year-old male was referred for management of oral cGVHD. He completed HCT in 2004 for chronic myelogenous leukemia. He had cGVHD with dry mouth, increased dental caries, and oral sensitivity affecting diet. When seen in December 2018 for oral changes, he was off all systemic immunosuppressive therapy. He had extensive lichenoid striations involving the buccal mucosa and tongue with plaque-like changes on the lateral borders of the tongue with isolated moderate to severe erythema.

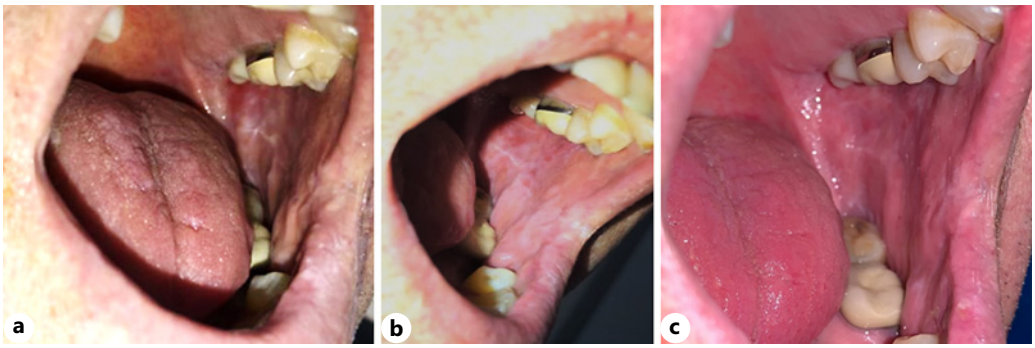

Fig. 2. Patient had secondary AML from prior myelofibrosis in June 2019 and underwent HCT from an unrelated donor with no acute or cGVHD. **a** In early February 2021 patient presented with mild oral GVHD. **b** Patient received first dose of Moderna vaccine (mRNA-1273) on February 16, 2021 and presented with prominent white lichenoid lesions on March 09, 2021. **c** Patient showed improvement in oral GVHD at subsequent visit on March 24, 2021.

He was prescribed topical vitamin A, cevimeline, and fluconazole due to culture-confirmed candidiasis. At follow-up, he had marked improvement with normal volume of saliva, reduction in erythema, and plaque-like changes. Following improvement, regular follow-up was conducted on a 6-month basis, and he maintained minimal lichenoid changes without erythema, normal saliva, and resolution of clinical candidiasis. After 6 months, fluconazole was discontinued. He was diagnosed in December 2020 with COVID-19 with severe flu-like and respiratory symptoms but avoided hospital admission and recovered after 3 weeks. He then received Pfizer (BNT162b2) vaccines, the first dose in March and second dose in April 2021. He experienced mild fatigue, muscle and joint pain, and low-grade fever that he stated resolved in 8 h. He then became aware of increased thickness of white changes on the left side of the tongue. In July 2021, oral findings included lichenoid striations, patchy moderate erythema, but increased plaque-like changes on the left lateral tongue, involving the entire lateral border with mild thickness, and palatal gingiva in the upper molar regions. These findings were much more prominent than oral findings seen in November 2020. Local therapy with increased vitamin A, cevimeline, a cholinergic agonist, resuming fluconazole and beginning turmeric was recommended. Oral symptoms resolved but mild change oral lesions persisted. At 1 month post vaccination, the status of oral cGVHD flare was seen. The CARE Checklist has been completed by the authors for these case reports, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533821).

Discussion

We present 4 cases of oral cGVHD flare temporally following vaccination for SARS-CoV-2. We believe this study represents the first report of new oral cavity changes or aggravation of oral GVHD following Pfizer (BNT162b2) or Moderna (mRNA-1273) vaccines in patients with prior allogeneic stem cell transplant. In these cases, two had oral, skin, and liver function changes, suggesting relation to vaccination. In one retrospective study of GVHD post-HCT, 3.5% were identified with flare in GVHD [4]. The cases showed oral with/without skin cGVHD following SAR-CoV-2 vaccines. Diagnosis and increase in symptoms were noted in patients leading to a need for local oral and potentially systemic management. Awareness of this diagnosis for post-transplant patients may facilitate local oral management if GVHD does flare after SARS-CoV-2 vaccination. Management of cases included local/regional oral treatments

with steroid, tacrolimus/pimecrolimus, and symptom management in addition to adjustment systemic immunosuppression. Oral management may include topical steroids or topical calcineurin inhibitors [8, 9]. Withholding immunosuppression taper during and immediately after COVID-19 vaccination will probably be helpful to prevent new or worsening GVHD.

These cases suggest that host response to SARS-CoV-2 vaccination may aggravate prior oral immune reactions and can lead to de novo presentation of oral immune conditions not previously identified, or activation of prior oral GVHD. Management of oral involvement results in control of inflammation and mucosal changes and enhanced systemic therapy when associated with flare in systemic GVHD.

As COVID-19 vaccination is strongly recommended and booster vaccine is now recommended, it is important to recognize the risk of flare of oral changes as de novo immune-mediated oral conditions may arise and require management. Patients must be counseled on risks when they receive any vaccine, and health care providers managing patients with GVHD must be aware of the potential to stimulate oral GVHD.

Acknowledgments

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Statement of Ethics

The study was approved by the City of Hope Internal Review Board under IRB 07047. All procedures were performed in accordance with the ethical standards of the City of Hope, the National Research Ethics Committee, and the 1964 Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice and later amendments or comparable ethical standards. Written informed consent was obtained from the patients for publication of these case reports and any accompanying images.

Conflict of Interest Statement

Dr. Nakamura received consulting fees from Bluebio, Sanofi, and Omeros; is on the speaker bureaus for Viracor, Magenta, and Kadmon; and is a member of the NCCN Panel for Hematopoietic Cell Transplantation. Dr. Ali received consulting fees from Incyte and BMS; is on the speaker bureaus for Incyte and BMS; and is a member of the NCCN Panel for MPN. The other authors declare that they have no competing interests.

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Author Contributions

Conceptualization, supervision, writing – original draft preparation, J.B.E.; methodology and validation, J.B.E, R.H., R.N., H.A.; writing – review and editing, J.B.E, R.H., R.N., S.E.Y., H.A.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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