Case Reports in Oncology

Case Rep Oncol 2015;8:369–377

DOI: 10.1159/000438747
Published online: August 19, 2015

1662–6575/15/0082–0369$39.50/0
www.karger.com/cro

Karger Open access

Recognition and Management of Oral Mucosal Injury Caused by Mammalian Target of Rapamycin Inhibitors: A Case Series

Timothy F. Meiller Sharon Varlotta Dianna Weikel

Department of Oncology and Diagnostic Sciences at University of Maryland School of Dentistry, University of Maryland Marlene and Stewart Greenebaum Cancer Center, University of Maryland Medical System, Baltimore, Md., USA

Key Words
Stomatitis · Mammalian target of rapamycin inhibitors · Recognition · Management

Abstract
The mammalian target of rapamycin inhibitors (mTORIs) everolimus and temsirolimus are approved by the US Food and Drug Administration (FDA) for the treatment of various forms of advanced cancer, and the mTORI sirolimus is approved as an immunosuppressive agent for the prophylaxis of organ rejection in patients receiving renal transplants. The oral lesions associated with mTORI toxicity are distinct from the well-documented chemotherapy- and radiotherapy-induced mucositis, but they may often be misdiagnosed by medical oncologists or transplant physicians, potentially resulting in inappropriate management of this complication. mTORI-associated oral mucosal injury appears to be dose related, and its onset is consistently earlier than conventional mucositis associated with chemotherapy or radiation therapy. Although the lesions appear to resolve within approximately 2 weeks and do not seem to recur as severely with subsequent courses of therapy, the reduction in a patient's quality of life as a result of oral pain that affects the intake of nutritional foods should be taken into consideration. We report three cases that illustrate the complexity involved in the early assessment, referral, and appropriate management of mTORI-associated oral mucosal injury. Corticosteroids appear to be very useful in managing and perhaps preventing these lesions, whereas this approach has never shown efficacy in conventional chemotherapy-related mucositis. Early intervention to reduce the mTORI-associated oral mucosal injury is important

KARGER 125

Timothy F. Meiller, DDS, PhD
University of Maryland
650 W. Baltimore St.
Baltimore, MD 21201 (USA)
E-Mail tfmeiller@umaryland.edu

to diminish the need for dose alterations of mTORIs and, therefore, to improve patient outcomes.

Introduction

Mammalian target of rapamycin inhibitors (mTORIs) represent a class of drugs that exhibit immunosuppressive and antiproliferative properties [1, 2]. This has resulted in their approval by the US Food and Drug Administration (FDA) as immunosuppressant therapies following organ transplantation and, more recently, for the treatment of numerous malignancies [1, 2]. Initially, rapamycin (sirolimus) was developed as an antifungal drug against *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* [1]. Years later, the potent immunosuppressive properties of rapamycin were detected, resulting in its FDA approval as an immunosuppressant therapy for the prevention of renal transplant rejection [3]. The development of rapamycin as an anticancer agent began in the 1990s with the discovery of temsirolimus [4], a novel soluble rapamycin derivative that subsequently became the first FDA-approved mTORI for the treatment of advanced renal cell carcinoma based on the findings of a pivotal phase III trial [4]. Rapamycin 'rapalogs', such as temsirolimus, everolimus, and ridaforolimus, are associated with improved pharmacokinetics and manageable immunosuppressive effects [5], and temsirolimus and everolimus have since been FDA approved for various malignancies [6, 7]. The therapeutic effects of rapamycin rapalogs are generally similar to that of rapamycin, but these derivatives are more hydrophilic and can often be administered either orally (everolimus) or intravenously (i.e., temsirolimus and ridaforolimus) [8].

The adverse effects associated with mTORIs such as rapamycin, temsirolimus, and everolimus are well characterized [3, 6, 7], and medical oncologists and transplant physicians are generally aware of the potential oral complications associated with mTORIs. The incidence of these complications vary according to the clinical setting, with sirolimus-associated oral mucosal injury rates (all grades) of less than 20% in renal transplant recipients [3] and everolimus-associated stomatitis rates (all grades) as high as 44% in patients with renal cancer [7]. This marked difference may be related to the use of mTORIs at lower doses in the posttransplantation treatment setting [3, 7]. However, mTORI-associated oral mucosal injury has often been termed 'mucositis' (potentially confusing the lesions with standard chemotherapy-induced lesions) or 'stomatitis', and has also been mistaken as oral symptomatology associated with conditions such as xerostomia, glossodynia, overall oral dysfunction, and even premalignancy. The difficulty in determining the appropriate terminology and accurately identifying mTORI-associated oral mucosal injury can lead to misdiagnosis by medical oncologists or transplant physicians, potentially resulting in inappropriate management of this complication.

Case Series

Here, we report three cases seen in the oral medicine program at the University of Maryland that illustrate the complexity involved in the early assessment, referral, and appropriate management of mTORI-associated oral mucosal injury.

Case 1

The patient was a 46-year-old male with pancreatic cancer who was receiving treatment with everolimus at a daily dose of 10 mg. This medication was started approximately 8 weeks prior to his referral to the oral medicine program for evaluation of severe herpetiform-like oral ulcerations on the lateroventral tongue (fig. 1) that were extremely painful, resulting in a reduction in normal nutritional intake.

After an initial assessment and history of the patient was undertaken, it was determined that these oral ulcerations were related to the initiation of everolimus therapy, and an appropriate discussion with his physician ensued. However, the patient succumbed to disease progression prior to initiation of an appropriate planned therapeutic regimen to manage his ulcerations that would have comprised the use of topical steroid applications to the oral lesions. Although the poor outcome of this patient was not attributed to the mTORI-associated oral complication, this case clearly supports the need for prevention protocols to improve quality of life regardless of disease prognosis.

Case 2

The patient was a 39-year-old female renal transplant recipient who was receiving sirolimus at a prescribed daily dose of 2 mg following transplantation, which had been completed approximately 100 days prior to her referral. She had begun to develop oral ulcerations 3 months after renal transplantation and previous treatment with cyclosporine. The patient presented with ulcerations on the lateral tongue (fig. 2a) and lower lip vestibule (fig. 2b) and was referred to the oral medicine program. It was determined that sirolimus was the most likely cause of the oral ulcerations, and the patient was prescribed topical clobetasol ointment applied locally to the oral ulcers. This approach was selected due to the anterior location of the lesions. The ulcer on the lower lip responded quickly to the topical clobetasol ointment, showing resolution in less than 10 days of therapy. Although the ulceration on the tongue reduced in size following treatment with the ointment, it continued to persist and caused a considerable reduction in quality of life. The transplant physicians have not planned any alterations in therapies for the patient, and she has not been to any follow-up appointments in the oral medicine department.

Case 3

The patient was a 75-year-old female who was referred from a local hospital to the oral medicine program for what were thought to be premalignant oral lesions. She had been diagnosed with hormone receptor-positive breast cancer 5 years prior to referral and had recently been treated with letrozole, demonstrating minimal response. A course of everolimus at 10 mg/day was started, and oral ulcers began to develop approximately 10 days after treatment initiation. The subject was evaluated and presented with a large (approx. 1.0 × 1.0 cm), irregular oral ulcer on the lower lip and two small adjacent lesions (fig. 3a). After her complete history was taken, a presumptive diagnosis of mTORI-associated oral mucosal injury was made. The diagnosis was discussed by phone with her oncologist, and the immediate thought was to reduce or discontinue the everolimus. We advised the oncologist that we would try a course of topical steroid and later determine whether any change in cancer therapy should be considered. The patient was prescribed dexamethasone elixir 0.5 mg/5 ml and was instructed to rinse with 5 ml of this solution 4 times daily, holding the liquid intraorally for 2–5 min before expectorating. The patient had near-complete resolution of the ulcerations after 1 week of this therapy and was completely ulcer free after 2 weeks. There was no dose reduction in her everolimus therapy, but she developed a second ulcer episode on the tongue approximately 4 weeks later (fig. 3b), but this resolved after an additional 2

Case Rep Oncol 2015;8:369–377
DOI: 10.1159/000438747

weeks of treatment with dexamethasone elixir. She is currently continuing with this rinse regimen twice daily and has remained ulcer free for 3 months since resolution of the initial lower lip ulcerations. As of this writing, the patient has maintained her cancer treatment.

Discussion

Conventional oral mucositis initiated by high-dose chemotherapy or radiotherapy has been studied and described over many years [9]. The expression of oral mucosal injury observed in association with mTORIs [10] and tyrosine kinase inhibitors, including erlotinib, sorafenib, and sunitinib, is unique [11]. The oral lesions associated with mTORI toxicity are distinct from chemotherapy- and radiotherapy-induced mucositis, and its onset is consistently earlier than that seen with conventional mucositis [10]. These mucosal ulcerations are considered an adverse effect related to the mTORI drug class. The oral lesions associated with mTORIs appear to resolve within approximately 2 weeks and do not seem to recur as severely with subsequent courses of therapy. The experience with mTORI-associated oral mucosal injury in transplant patients supports the view that dose adjustments are not usually warranted [12]. Clinicians must always consider how significantly the effects of oral ulcerations alter the patient's quality of life.

The mTORI-associated oral lesions present as multiple or singular ulcerations that are usually small, are generally less than 0.5 cm in diameter, and may be present primarily in the anterior third of the oral cavity [10]. However, larger lesions and those extending into the tonsillar pillar regions are not uncommon. Pain is a consistent finding in all types of mucosal injury, and some of the smaller but multiple, deep ulcerations found in mTORI-associated oral mucosal injury may be significantly painful and affect nutritional intake. The lesions resemble the relatively common condition of recurrent aphthous ulceration (RAU) and usually present as either the minor form of RAU or herpetiform RAU [10]. T-cell responses have been shown in RAU [13] to be involved in the pathogenesis of the lesions and should be included in future studies of mTORI-associated oral mucosal injury. Corticosteroids appear to be very useful in managing and perhaps preventing the lesions, whereas this approach has never shown efficacy in conventional chemotherapy-related mucositis [14]. A retrospective analysis of cancer patients treated with everolimus or ridaforolimus reported clinical improvement in most patients (87%) with mTORI-associated stomatitis after treatment with interlesional, topical, or systemic corticosteroid therapy [15]. This is consistent with the report that clobetasol reduced aphthous ulceration in renal transplant patients receiving sirolimus [14].

Conclusion

These three case reports illustrate the complexity of dealing with the oral complications of targeted cancer and posttransplant therapies, and specifically mTORI-associated oral mucosal injury. Because mTORIs are approved for numerous cancer treatment applications and are usually given at higher doses than have previously been used in organ transplant recipients, the incidence of associated mucosal injury will be more commonly recognized in the future. With these three sample cases, we have highlighted the need for education of patients, early and accurate recognition by the oncology and transplant teams, and early referral to an oral care professional experienced in the management of these types of conditions (table 1). Once identified, therapeutic interventions should be initiated and continued as

needed. Future study of prevention protocols to identify risk, response, and appropriate medication approaches should be conducted. Early intervention to treat and then possibly prevent the mucosal injury can have important effects in reducing the need for mTORI dose alterations and, therefore, may help to improve therapeutic goals.

Acknowledgements

The authors thank Matthew Grzywacz, PhD, of ApotheCom (Yardley, Pa., USA) for editorial and technical assistance in the development of this paper. Novartis Pharmaceuticals Corporation provided funding for the editorial review of this paper.

Statement of Ethics

On behalf of my co-authors, I attest that the patients described in this case study entitled 'Recognition and Management of Oral Mucosal Injury Caused by Mammalian Target of Rapamycin Inhibitors: A Case Series' provided informed consent to use this information for the case study. The project was reviewed and had full approval of the Institutional Review Board of the University of Maryland, Baltimore, Md., USA.

Disclosure Statement

T.F. Meiller, S. Varlotta, and D. Weikel are investigators on a clinical trial sponsored by Novartis Pharmaceuticals Corporation that is studying the effects of mTORIs on oral tissues.

References

1 Ponticelli C: The pros and the cons of mTOR inhibitors in kidney transplantation. Expert Rev Clin Immunol 2014;10:295–230.
2 Gomez-Pinillos A, Ferrari AC: mTOR signaling pathway and mTOR inhibitors in cancer therapy. Hematol Oncol Clin North Am 2012;26:483–505.
3 Wyeth Pharmaceuticals: Rapamune (sirolimus) oral solution and tablets (package insert). Philadelphia, Wyeth Pharmaceuticals, 2015.
4 Hudes G, Carducci M, Tomczak P, et al: Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271–2281.
5 Faivre S, Kroemer G, Raymond E: Current development of mTOR inhibitors as anticancer agents. Nat Rev Drug Discov 2006;5:671–688.
6 Wyeth Pharmaceuticals: Torisel Kit (temsirolimus) injection, for intravenous infusion only (package insert). Philadelphia, Wyeth Pharmaceuticals, 2015.
7 Novartis Pharmaceuticals Corporation: Afinitor (everolimus) tablets for oral administration. Afinitor Disperz (everolimus tablets for oral suspension) (package insert). Hanover, Novartis Pharmaceuticals Corporation, 2015.
8 Tsang CK, Qi H, Liu LF, et al: Targeting mammalian target of rapamycin (mTOR) for health and diseases. Drug Discov Today 2007;12:112–124.
9 Sonis ST: Oral mucositis. Anticancer Drugs 2011;22:607–612.
10 Sonis S, Treister N, Chawla S, et al: Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. Cancer 2010;116:210–215.
11 Dy GK, Adjei AA: Understanding, recognizing, and managing toxicities of targeted anticancer therapies. CA Cancer J Clin 2013;63:249–279.
12 Kaplan B, Qazi Y, Wellen JR: Strategies for the management of adverse events associated with mTOR inhibitors. Transplant Rev (Orlando) 2014;28:126–133.

13 Preeti L, Magesh K, Rajkumar K, et al: Recurrent aphthous stomatitis. J Oral Maxillofac Pathol 2011;15:252–256.
14 Chuang P, Langone AJ: Clobetasol ameliorates aphthous ulceration in renal transplant patients on sirolimus. Am J Transplant 2007;7:714–717.
15 de Oliveira MA, Martins E, Martins F, Wang Q, et al: Clinical presentation and management of mTOR inhibitor-associated stomatitis. Oral Oncol 2011;47:998–1003.

Table 1. Recommendations for the prevention and management of mTORI-associated oral mucosal injury

Patient education prior to initiation of mTORI therapy
Prompt reporting
Educate patient on common signs and symptoms
Contact physician at first sign of mouth discomfort
Contact physician if lesions occur that interfere with eating or drinking
Consistent, regular, and thorough brushing with a soft toothbrush; flossing after each meal; frequent rinsing with bland rinses such as sterile water, normal saline, or sodium bicarbonate; use of oral moisturizers
Avoid alcohol-containing over-the-counter rinses and toothpastes with sodium lauryl sulfate
Avoid alcohol- or peroxidase-containing mouthwash products
Avoid acidic, spicy, hard, or crunchy foods, and consume foods that are tepid rather than hot
Stress the need for regular dental examinations
Treat anticipated infections (e.g., periodontal disease)
Evaluate for herpetic and fungal infections, and administer antivirals (e.g., acyclovir) and antifungals (e.g., fluconazole) as appropriate
Treatment options
Dexamethasone 0.5 mg/5 ml[a]
500 ml bottle
5–10 ml, swish and hold for 2–5 min and expectorate; repeat 3–6 times daily
Refills: as needed
Clobetasol ointment, cream, or gel (select on patient preference)[b]
60 g tube
Apply locally as directed 3–4 times daily
Refills: as needed

[a] Topical rinse applications such as this are useful when lesions are numerous or located in the posterior aspects of the oral cavity.
[b] Topical applications such as this are useful only when there are one or two lesions that are easily accessible with a cotton swab applicator (i.e., near the anterior of the oral cavity).

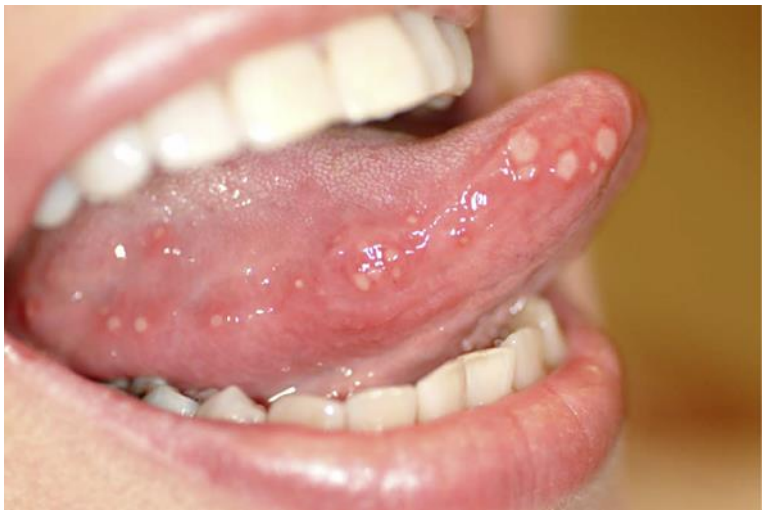

Fig. 1. Case 1. Herpetiform-like oral ulcerations on the lateroventral tongue.

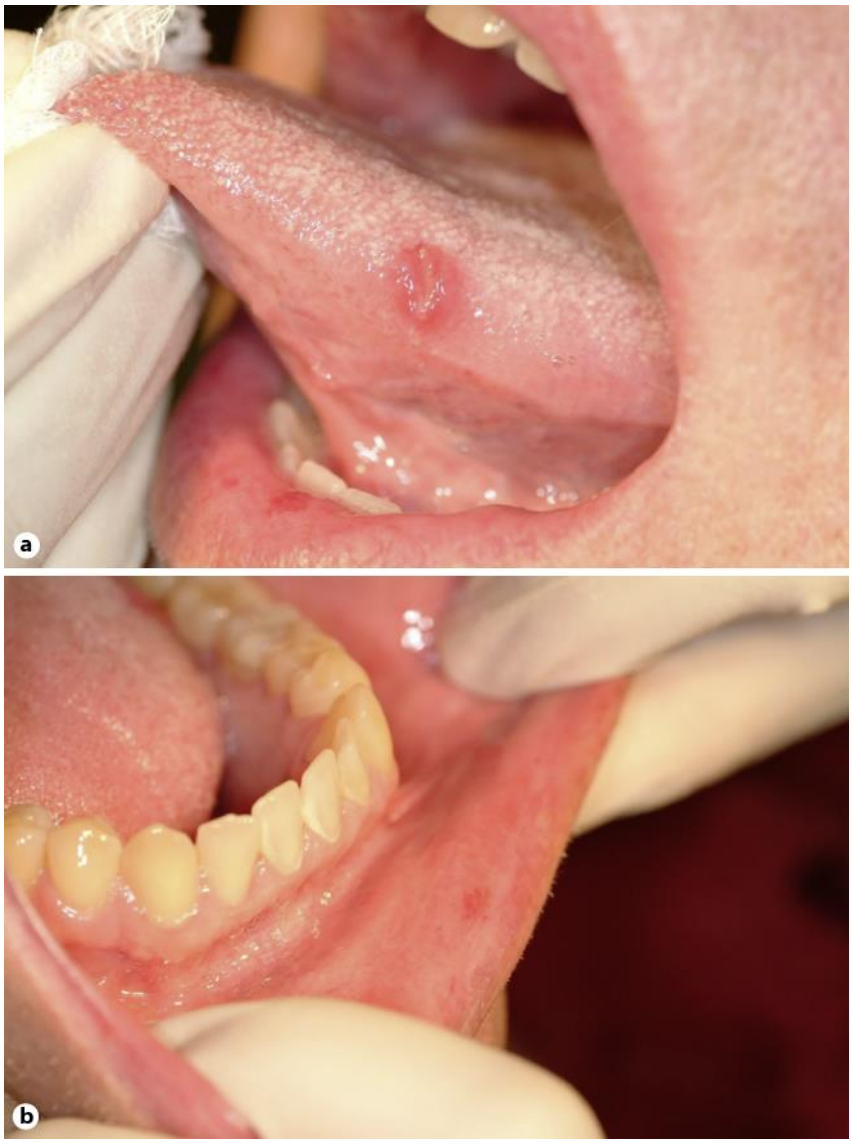

Fig. 2. Case 2. The patient presented with ulcerations on the lateral tongue (**a**) and lower lip vestibule (**b**).

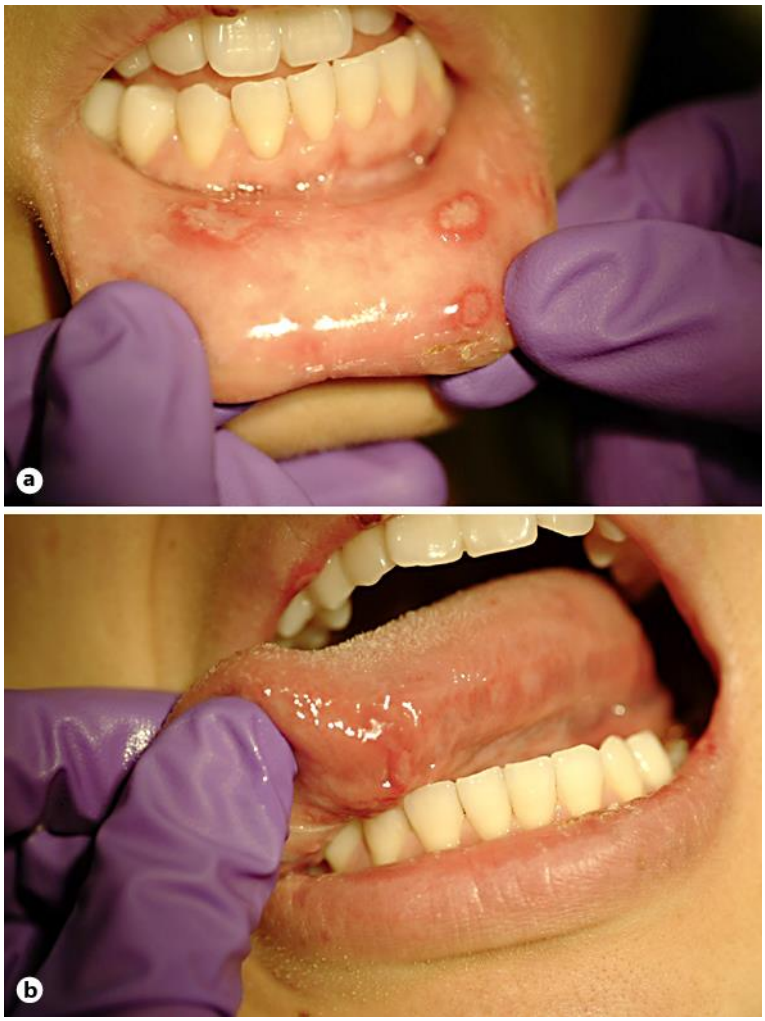

Fig. 3. Case 3. Large (approx. 1.0 × 1.0 cm), irregular oral ulcer on the lower lip and two small adjacent lesions at presentation (**a**), and on the tongue during the second ulcer episode approximately 4 weeks later (**b**).