

EDITOR'S
CHOICE

CASE REPORT

Everolimus-associated stomatitis in a patient who had renal transplant

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SUMMARY

Everolimus is used as an immunosuppressant in renal allograft transplant rejection and in metastatic breast cancer treatment. One side effect of everolimus is stomatitis, referred to as mammalian target of rapamycin inhibitor-associated stomatitis. This side effect can affect treatment course and contribute to discontinuation of therapy or dose reduction, previously reported in the treatment of metastatic breast cancer. Here, we present a case of everolimus-associated stomatitis with a novel management method with intralesional triamcinolone that allows for continuous course of everolimus.

BACKGROUND

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor derived from sirolimus, originally produced by *Streptomyces hygroscopicus*.¹ Everolimus reduces the activity of mTOR by binding to FK-binding protein, thereby preventing cell cycle progression and proliferation.¹ Everolimus is an FDA-approved agent for advanced breast cancer and pancreatic neuroendocrine tumours.² It is also used as an immunosuppressant in renal allograft transplant rejection.³ Preclinical models show that everolimus prevents acute rejection of kidney transplants and reduces rejection.⁴ Vascular remodelling in transplant allografts is suggested to be part of graft dysfunction.⁴ Everolimus prevents this process from occurring by inhibiting smooth muscle cell proliferation and reducing intimal thickening process.⁴

One of the side effect of everolimus, and other mTOR inhibitors, is oral stomatitis.⁵ mTOR inhibitor-associated stomatitis (mIAS) can significantly affect the treatment course and may contribute to discontinuation of therapy.⁶ mIAS has been reported to range from 43% to 70%.^{5 7 8} Other side effects of everolimus include nasopharyngitis, shortness of breath and acne-like lesions.⁷ de Oliveira *et al*⁶ describe a case series revealing five patients required discontinuation of treatment due to stomatitis and five patients required dose reductions of everolimus secondary to stomatitis in the course of their cancer treatment. Reduction in dose or discontinuation of everolimus may compromise optimal outcomes, such as graft survival in patients who had renal transplants.⁹ Everolimus is used in renal transplant to prevent graft rejection and is associated with a lower risk of cytomegalovirus infections compared to rapamycin or sirolimus, a common concern in patients who had transplants.⁹

Everolimus can be used in renal allograft transplantations.³ This requires new approaches to address everolimus-associated stomatitis.^{9 10} Here, we describe a useful management strategy for symptomatic treatment and prophylaxis of mIAS in a patient who had renal transplant.

CASE PRESENTATION

A 48-year-old female was referred to the Division of Oral Medicine and Dentistry at Brigham and Women's Hospital for 'painful oral swelling'. The patient presented with persistent pain in the lower mandibular region and tongue for 5 days. Medications at time of the Oral Medicine consult included everolimus 0.75 mg two times per day, metoprolol 25 mg two times per day, methylprednisolone 4 mg once daily, valganciclovir 900 mg two times per day and ergocalciferol 50 000 units once weekly. Her medical history was significant for hypertension, anaemia, hyperlipidaemia and end-stage renal disease secondary to polycystic kidney disease. The patient underwent a renal transplant from a living unrelated donor 364 days prior. The donor was cytomegalovirus (CMV)-positive and the recipient was CMV-negative. Throughout the entire postoperative course, the patient was leucopenic. Prophylactic valganciclovir was discontinued 6 months after transplantation to improve the leucocyte count. Forty-five days after discontinuing valganciclovir, the patient developed CMV viraemia and CMV colitis. The patient was switched to everolimus 0.75 mg two times per day from tacrolimus 4.5 mg two times per day that the patient had been on since the transplant, because of potential anti-CMV effects of everolimus.^{11 12} The patient developed discomfort on the right mandibular area for 42 days after starting everolimus. At the time of the visit, everolimus was therapeutic at 6.1 ng/mL



Figure 1 Everolimus-associated stomatitis.



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Table 1 Cases of mIAS secondary to everolimus use that describes management strategies

Author (year)	Type of article	Disease	mTOR	Dosage	Intervention	Duration	Discussion
Kalogirou <i>et al</i> ¹³ (2014)	Case series	Renal cell carcinoma and breast cancer	Everolimus	5 mg qd 10 mg qd	Magic Mouthwash* four times daily	3–15 days	mIAS healed in 3–15 days.
Nicolatou-Galitis <i>et al</i> ¹⁵ (2013)	Case series	HER2+ breast cancer	Everolimus	10 mg qd	Dexamethasone solution 0.5 mg/mL and miconazole 2% gel (1–2 weeks), four patients discontinued everolimus	1–2 weeks	Ulcers healed within 1–2 weeks of either discontinuing everolimus or treatment with dexamethasone solution and miconazole gel
de Oliveira <i>et al</i> ⁶ (2011)	Case series	Cervical chordoma, leiomyosarcoma, osteosarcoma, spindle cell sarcoma, liposarcoma, merkel cell carcinoma, thyroid carcinoma, Waldenstrom macroglobulinaemia	Everolimus Ridaforolimus	10 mg 12.5 mg 40 mg	Topical anaesthetics, Magic Mouthwash†, clobetasol gel 0.05%, dexamethasone 0.1 mg/mL, triamcinolone paste, intralesional triamcinolone, systemic prednisone (1 mg/kg for 7 days)	Variable	Median time to onset of ulcers was 10 days. One of 17 patients discontinued therapy due to mIAS. Five of 17 had dose reductions due to mIAS.
Ferté <i>et al</i> ¹⁷ (2011)	Chart review	Non-small-cell lung cancer, small-cell lung cancer or breast cancer	Everolimus	Ranged from 2.5 mg qd to 10 mg qd, or 20 mg qw to 30 mg qw	Sodium bicarbonate-based mouthwash, oral fluconazole	Variable	Patients with prior chemotherapy or receiving higher doses of everolimus had higher rates of ulcers and for longer durations. Ten per cent of patients required dose delay because of mIAS and 9% required dose reduction due to mIAS. Empirical treatment with sodium bicarbonate-based mouthwash, oral fluconazole, did not show improvement in mIAS within 5 days after onset.
Sahin <i>et al</i> ¹⁸ (2011)	Retrospective chart review	Patients who had renal transplant switched from calcineurin-based therapies to sirolimus or everolimus	Sirolimus Everolimus	NA	NA	NA	Reducing calcineurin inhibitor-based therapy, switching to sirolimus or everolimus, was beneficial for GFR
Vermeulen <i>et al</i> ¹⁹ (2010)	Case report	Severe stomatitis in a patient who had cardiac transplant after switching to everolimus	Everolimus		Local anaesthetic	Not specified	Oral local anaesthetics used but no effect on aphthous ulcers; required discontinuing everolimus secondary to mIAS, requiring conversion to cyclosporine and azathioprine
De Simone <i>et al</i> ²⁰ (2009)	Prospective	40 patients who had renal transplants	Everolimus	0.75 mg BID	NA	NA	Everolimus can be used in place of a calcineurin inhibitor-based therapy in patients with liver allograft without a decrease in efficacy.
Ram <i>et al</i> ²¹ (2008)	Case report	Patients who had renal transplant on sirolimus switched to everolimus	Everolimus	0.75 mg BID	Sirolimus switched to everolimus		Patient developed aphthous ulcers on sirolimus and then switched to everolimus. Aphthous ulcers subsequently resolved.
Peterson <i>et al</i> ²² (2016)	Literature review	NA	Everolimus Temozolomide Ridaforolimus Sirolimus	NA	Preventative steroid mouth rinses (NCT02069093)	NA	mIAS can affect the delivery of mTOR inhibitor therapy.
Boers-Doets <i>et al</i> ¹⁴ (2013)	Literature review	NA	mTOR inhibitors	NA	NA	NA	mIAS are frequent side effects in patients with cancer with genes playing a potential role.

*Magic Mouthwash (lidocaine gel 2%×30 g, doxycycline suspension 50 mg/5 mL×60 mL and sucralfate oral suspension 1000 mg/5 mL dissolved in sodium chloride 0.9%×2000 mL).¹³

†Magic Mouthwash (lidocaine, aluminium hydroxide, magnesium hydroxide, dimethicone suspension, diphenhydramine, equal parts).

BID, two times a day; GFR, glomerular filtration rate; HER2, human estrogen receptor 2; mIAS, mTOR inhibitor-associated stomatitis; mTOR, mammalian target of rapamycin; qd, four times a day; qw, every week.

(range 3–8 ng/mL). The patient denied fever or malaise and reported four small raised areas on the right aspect of the tongue. The patient described a constant aching pain and a 5/10 burning sensation which increased to 7/10 when swallowing. The intraoral examination revealed a 3 cm × 3 cm aphthous-like ulcer with erythematous borders of the right posterior ventral tongue (figure 1). There was a slight right submandibular swelling with pain on palpation. Differential diagnosis included neutropenic ulcer, herpes simplex virus (HSV)-associated ulcer and mTOR inhibitor-associated ulcer. At the time of the first consult, the patient was leucopenic and thrombocytopenic (WCC: 0.71 K/ μ L, platelets: 63 K/ μ L). The patient remained leucopenic throughout the course of the development of these ulcers. Prior to starting everolimus, the patient did not develop any ulcers. A diagnosis of mIAS was made based on timeline of starting everolimus and clinical presentation of the ulcer consistent with the diagnosis. The ulcer was injected with 32 mg of triamcinolone, and the patient was prescribed clobetasol 0.05% gel to apply to affected areas three times daily and benzocaine gel as needed for pain. A 29-gauge needle was inserted into the lesion and aspirating prior to injection of triamcinolone to ensure avoidance of any arteries. Triamcinolone (32 mg) was then injected into the lesion. 0.1–0.2 mL is injected per square centimetre of involved mucosa. On 2-week follow-up, the patient reported 95% improvement in symptoms and used the clobetasol 0.05% gel as directed. One hundred and eighty-one days after follow-up, the patient reported that the prophylactic clobetasol gel continues to offer tremendous relief in preventing the ulcers.

OUTCOME AND FOLLOW-UP

This case report outlines an effective management therapy for mIAS in a patient with renal allograft. The patient presented with a constellation of symptoms that can be mistaken for strep throat, an HSV ulcer or neutropenic ulcer. Here, we suggest intralesional steroid injections and topical steroid applications as an effective therapy for management of everolimus-associated oral ulcers. Management of everolimus-associated ulcers requires an interdisciplinary approach involving transplantation medicine, oral medicine and nephrology to provide optimal outcomes.

DISCUSSION

Summary of results and diagnosis

This case report highlights management strategies of mIAS in a patient with a history of renal transplant. The patient presented with a large aphthous-like ulcer on the right tongue that was successfully managed with intralesional triamcinolone 0.05% and topical clobetasol gel 0.05% with reduction in pain. mIAS presents as oral ulcerations characterised by a greyish-white pseudomembrane that are distinct from chemotherapy-associated mucositis (figure 1).⁶ The size and clinical presentation of the ulcer on the tongue was suggestive of an mTOR inhibitor-associated ulcer secondary to everolimus use. It is less likely that it was a neutropenic ulcer as the patient was leucopenic throughout postoperative course and did not present with ulcers prior to starting everolimus.

While there are no definitive data suggesting mIAS, the timeline and clinical presentation with history are congruent with the diagnosis of mIAS. Treatment was based empirically on clinical presentation and onset. It is possible that the combination of leucopenia and mTOR inhibitor use contributed to the development of these lesions.

Stomatitis is a known adverse effect of mTOR inhibitors, which was initially reported in the EXIST-1, RADIANT-3 and

BOLERO-2 trials.⁸ A meta-analysis of the incidence of stomatitis with everolimus use reveals a rate of 67% in solid tumour trials and 70% in tuberous sclerosis trials.⁸ Stomatitis did not affect progression-free survival.⁸ Of note, oncological dosing of everolimus is often multiple-fold higher than transplant dosing of everolimus; therefore, these rates are not necessarily reflective of stomatitis rates in patients who had transplants.^{8 13} Previous literature suggests that dose reductions were required in patients with cancer for grade 2 and 3 stomatitis, with one patient discontinuing cancer treatment.⁶ Literature has suggested that most cases of mIAS are generally mild and self-limiting, not requiring any treatment.¹⁴ As we cannot determine which lesions will be self-limiting, the quality of life leading to this determination can be poor, leading to complications such as malnutrition and dose reduction of medically necessary treatment. The method we present here allows for prevention of complications early on. It will be up to the providers' best judgement whether intervening with a corticosteroid injection would be beneficial to the patient as there are no predictor tools that can be used to determine which patients will develop large and painful lesions.¹⁴ Therefore, the provider must elicit the patient's input regarding pain and treatment of these lesions.

This is the first case of mIAS in a patient who had renal transplant. Previous case reports of mIAS have been reported in patients receiving high doses of everolimus for cancer treatment or liver transplants.^{15 16} Case series have described management of mIAS with Magic Mouthwash with the lesions resolving in 3–15 days in patients with renal cell carcinoma and breast cancer.¹³ Dexamethasone solution 0.5 mg/mL added to 6 mL of water three to four times/day with miconazole gel have been used in patients receiving everolimus for breast cancer with variable improvement in 1–2 weeks.¹⁵ Table 1 describes the various management strategies attempted to treat mIAS in the literature. There is variability in response to these treatments, with corticosteroids and local analgesics being a common management strategy.^{6–22} In these case reports, everolimus dosing was reduced to ameliorate the adverse effects. In the population of renal allograft, this may not be a desirable option as it increases the risk of transplant rejection. In our case, 40 mg of intralesional triamcinolone was effective and the everolimus dose was not adjusted.

Learning points

- ▶ Intralesional triamcinolone offers relief for everolimus-associated stomatitis.
- ▶ Topical clobetasol gel 0.05% can be applied to affected areas for potential prophylaxis and alleviation of symptoms.
- ▶ This combination treatment allowed for continuation of everolimus treatment without dose reduction secondary to stomatitis.

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Contributors YDJ wrote the manuscript and did the literature review. AV and AA saw the patient, treated the patient and edited the manuscript.

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