CASE REPORT

Everolimus-associated stomatitis in a patient who had renal transplant

Yisi D Ji,1 Ali Aboalela,2 Alessandro Villa3

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 Streptomyces hygroscopicus.1 It is also used as an immunosuppressant in renal allograft transplant rejection.2 Preclinical models show that everolimus prevents acute rejection of kidney transplants and reduces rejection.3 Vascular remodelling in transplant allografts is suggested to be part of graft dysfunction.4 Everolimus prevents this process 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.3 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%.578 Other side effects of everolimus include nasopharyngitis, shortness of breath and acne-like lesions.7 de Oliveira et al8 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 can be used in renal allograft transplantations.3 This requires new approaches to address everolimus-associated stomatitis.910 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 30 000 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 twice 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.1112 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.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Type of article</th>
<th>Disease</th>
<th>mTOR</th>
<th>Dosage</th>
<th>Intervention</th>
<th>Duration</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicolatou-Galitis et al (2013)</td>
<td>Case series</td>
<td>HER2+ breast cancer</td>
<td>Everolimus</td>
<td>10 mg qd</td>
<td>Dexemethasone solution 0.5 mg/mL and miconazole 2% gel (1–2 weeks), four patients discontinued everolimus</td>
<td>1–2 weeks</td>
<td>Ulcers healed within 1–2 weeks of either discontinuing everolimus or treatment with dexemethasone solution and miconazole gel</td>
</tr>
<tr>
<td>de Oliveira et al (2011)</td>
<td>Case series</td>
<td>Cervical chordoma, leiomyosarcoma, osteosarcoma, spindle cell sarcoma, liposarcoma, melker cell carcinoma, thyroid carcinoma, Waldenstrom macroglobulinaemia</td>
<td>Everolimus</td>
<td>10 mg</td>
<td>Topical anaesthetics, Magic Mouthwash†, clotetaxel gel 0.05%, dexemethasone 0.1 mg/mL, triamcinolone paste, intralesional triamcinolone, systemic prednisone (1 mg/kg for 7 days)</td>
<td>Variable</td>
<td>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.</td>
</tr>
<tr>
<td>Ferté et al (2011)</td>
<td>Chart review</td>
<td>Non-small-cell lung cancer, small-cell lung cancer or breast cancer</td>
<td>Everolimus</td>
<td>Ranged from 2.5 mg qd to 10 mg qd, or 20 mg qw to 30 mg qw</td>
<td>Sodium bicarbonate-based mouthwash, oral fluconazole</td>
<td>Variable</td>
<td>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.</td>
</tr>
<tr>
<td>Sahin et al (2011)</td>
<td>Retrospective chart review</td>
<td>Patients who had renal transplant switched from calcineurin-based therapies to sirolimus or everolimus</td>
<td>Sirolimus</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Reducing calcineurin inhibitor-based therapy, switching to sirolimus or everolimus, was beneficial for GFR</td>
</tr>
<tr>
<td>Vermeulen et al (2010)</td>
<td>Case report</td>
<td>Severe stomatitis in a patient who had cardiac transplant after switching to everolimus</td>
<td>Everolimus</td>
<td></td>
<td>Local anaesthetic</td>
<td>Not specified</td>
<td>Oral local anaesthetic used but no effect on aphthous ulcers; required discontinuing everolimus secondary to mIAS, requiring conversion to cyclosporine and azathioprine</td>
</tr>
<tr>
<td>De Simone et al (2009)</td>
<td>Prospective</td>
<td>40 patients who had renal transplants</td>
<td>Everolimus</td>
<td>0.75 mg BID</td>
<td>NA</td>
<td>NA</td>
<td>Everolimus can be used in place of a calcineurin inhibitor-based therapy in patients with liver allograft without a decrease in efficacy.</td>
</tr>
<tr>
<td>Ram et al (2008)</td>
<td>Case report</td>
<td>Patients who had renal transplant on sirolimus switched to everolimus</td>
<td>Everolimus</td>
<td>0.75 mg BID</td>
<td>Sirolimus switched to everolimus</td>
<td>NA</td>
<td>Patient developed aphthous ulcers on sirolimus and then switched to everolimus. Aphthous ulcers subsequently resolved.</td>
</tr>
<tr>
<td>Peterson et al (2016)</td>
<td>Literature review</td>
<td></td>
<td>Everolimus</td>
<td></td>
<td>Preventive steroid mouth rinses (NCT02069093)</td>
<td>NA</td>
<td>mIAS can affect the delivery of mTOR inhibitor therapy.</td>
</tr>
<tr>
<td>Boers-Doets et al (2013)</td>
<td>Literature review</td>
<td></td>
<td>Everolimus</td>
<td></td>
<td>mTOR inhibitors</td>
<td>NA</td>
<td>mIAS are frequent side effects in patients with cancer with genes playing a potential role.</td>
</tr>
</tbody>
</table>

*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).†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.
Triamcinolone (32 mg) was then injected into the lesion. A 0.129-gauge needle was inserted into the lesion and aspirating 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. The patient was prescribed clobetasol 0.05% gel to apply to affected areas three times daily and benzocaine gel as needed for pain. A patient was prescribed clobetasol 0.05% gel to apply to affected areas three times daily and benzocaine gel as needed for pain.

OUTCOME AND FOLLOW-UP
This case report outlines an effective management strategy 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 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.

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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The authors acknowledge the Department of Oral Medicine and Dentistry.

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

Competing interests
None declared.

Patient consent
Obtained.

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Not commissioned; externally peer reviewed.

(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 neutrophilic 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/µL, platelets: 63 K/µL). 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.

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