



## mTOR inhibitor-associated stomatitis (mIAS) in three patients with cancer treated with everolimus

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Mammalian targets of rapamycin inhibitors (mTOR inhibitors, mTORI) are indicated for the management of several cancer types, including hormone receptor–positive or HER2-negative breast cancer, advanced renal cell carcinoma, advanced neuroendocrine tumors of pancreatic origin, and tuberous sclerosis complex–related tumors. Among the most common adverse events of mTORI medication are discrete, large, solitary or multiple, superficial ulcers, almost exclusively situated on nonkeratinized oral mucosa, described as mTORI-associated stomatitis (mIAS). We describe the clinical presentation, course, and management of mIAS in three patients receiving the mTORI everolimus (Afinitor, Novartis, East Hanover, NJ). In two patients, mIAS manifested 9 and 30 days after first using everolimus, respectively, whereas in the third patient, it recurred 3 months after re-introduction of everolimus. Oral rinses with a “magic mouthwash” solution (dexamethasone oral drops solution 2 mg/mL × 10 mL, lidocaine gel 2% × 30 g, doxycycline suspension 50 mg/5 mL × 60 mL, and sucralfate oral suspension 1000 mg/5 mL × 150 mL, dissolved in sodium chloride 0.9% × 2000 mL) four times daily proved helpful in alleviating the symptoms, and the ulcers healed in 4 to 15 days. No side effects were recorded, and dose reduction or discontinuation of everolimus was not necessitated in two cases. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119: e13-e19)

Oral lesions represent one of the most common treatment-related and dose-limiting adverse events in patients receiving mTORI, which are the pharmacologic agents for the management of several cancer types.<sup>1-3</sup> These lesions are reported in patients managed with orally administered everolimus, indicated for advanced hormone receptor–positive or HER2-negative breast cancer, advanced neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, and tuberous sclerosis complex-related renal angiomyolipoma or subependymal giant cell astrocytoma; intravenously administered temsirolimus, indicated for advanced renal cell carcinoma; and intravenously or orally administered ridaforolimus that is currently under clinical investigation for the management of several malignancies.<sup>1,2,4,5</sup> In a recent review of 44 studies, including 2822 patients, the incidence of oral lesions was 52.9% for all mTORI, 44.3% for everolimus, 60.8% for temsirolimus, and 54.6% for ridaforolimus.<sup>1</sup> Various terms, such as stomatitis, mucositis, oral ulcers, mouth ulcerations, mucosal inflammation or stomatitis, mouth sores, aphthous stomatitis, aphthous-like oral

lesions, and ulcerative stomatitis, are used for the description of oral lesions in mTORI-treated patients.

Sonis et al.<sup>6</sup> introduced the term *mTORI-associated stomatitis* (mIAS) for the description of aphthous-like oral ulcers confined to the nonkeratinized, movable mucosa in patients with solid malignancies treated with ridaforolimus. This term has been adopted by most authors, as the generic term “mucositis/stomatitis” used in clinical trials of mTORI may refer to any inflammatory condition of oral tissue, including the mucosa, dentition or periapices, and periodontium, and to infections of oral tissues.<sup>7</sup> The term also distinguishes those lesions from the conventional cytotoxic oral mucositis caused by chemotherapy or radiotherapy.<sup>5</sup>

Clinically, mIAS presents with discrete, solitary or multiple, superficial, aphthous-like ulcers covered by a thin pseudomembrane and surrounded by a discrete erythematous halo, on the buccal and labial mucosa, lateral borders of the tongue, soft palate, and floor of mouth.<sup>2,3,5,6,8,9</sup> Small, large, and herpetiform ulcers are described.<sup>10</sup> The ulcers may be very painful and cause severe functional disturbance, adversely affecting the quality of life of the patients. Thus, dose reduction or

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### Statement of Clinical Relevance

Aphthous-like oral ulcers are a common adverse event of unknown pathogenesis, affecting patients receiving the mammalian target of rapamycin inhibitors for the management of cancer. These ulcers should be distinguished from the conventional chemotherapy- or radiotherapy-induced oral mucositis.

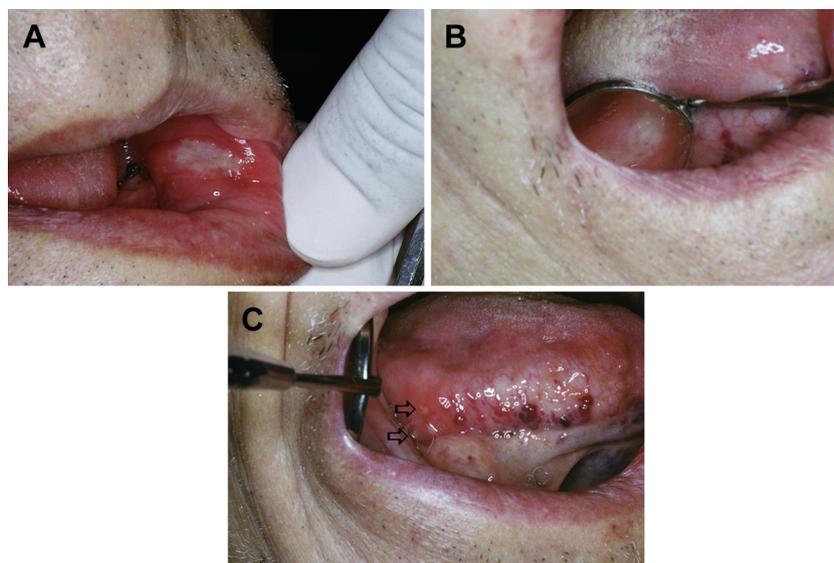


Fig. 1. (Case 1) Irregularly shaped superficial ulcers covered by a whitish pseudomembrane and surrounded by a diffuse erythematous halo (A) on the anterior left buccal mucosa, (B) the lingual mandibular mucosa, and (C) the right lateral border of the tongue (arrows).

even cessation of therapy may be necessitated, and a predisposition for local and systemic infections may ensue.<sup>5,8</sup> Digestive symptoms and cutaneous adverse events may coexist with mIAS.<sup>3,6</sup>

mIAS is a common and well-recognized adverse event of mTORI treatment in patients with cancer, but there are only a few case series with detailed descriptions of its clinical presentation, course, and management,<sup>2,9,10</sup> and clinical pictures may be found in some other studies.<sup>3,5,8,11-13</sup> We report two additional new cases of mIAS and provide follow-up of one previously described case.<sup>10</sup>

## CASE REPORTS

### Case 1

A 69-year-old man with advanced renal cell carcinoma, who had undergone nephrectomy in 2001, was initially treated with 75 mg/d sunitinib malate (Sutent, Pfizer, New York) for 3 months and then with 5 mg/d orally administered everolimus (Afinitor, Novartis, East Hanover, NJ). Nine days after starting everolimus, he developed “stomatitis,” which caused difficulty in talking and feeding. He removed his partial dentures and used “antiseptic mouthwashes” and miconazole nitrate oral gel without relief; therefore, on his oncologist’s advice, he discontinued everolimus 3 days before presentation. The patient’s medical record did not show any other disease, including recurrent aphthous ulcerations, and he denied smoking or use of any medications other than everolimus.

Clinically, irregularly shaped superficial ulcers, covered by a whitish pseudomembrane and surrounded by a diffuse erythematous halo, were found on the anterior left buccal mucosa (Figure 1, A), measuring 1.6 × 1.4 cm, on the lingual mandibular mucosa (Figure 1, B) measuring approximately 1 × 0.5 cm, and on the right lateral border of the tongue,

measuring approximately 0.1 cm in diameter (Figure 1, C). The root socket of a recently extracted tooth had healed normally. Cervical lymphadenopathy was not palpated. Complete blood count (CBC) revealed anemia (hemoglobin 10.8 g/dL, normal range 13-17 g/dL; hematocrit 31.7%, normal range 39%-52%) and mild thrombocytopenia (138 K/ $\mu$ L, normal range 140-440 K/ $\mu$ L).

A diagnosis of mIAS was rendered. According to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0), gastrointestinal adverse event “mucositis/stomatitis,” the severity was graded 2, as there were patchy ulcerations or pseudomembranes, and, although symptomatic, the patient could eat and swallow a modified diet (Table I).<sup>14</sup> Oral rinses with a “magic mouthwash” (dexamethasone oral drops solution 2 mg/mL × 10 mL, lidocaine gel 2% × 30 g, doxycycline suspension 50 mg/5 mL × 60 mL, and sucralfate oral suspension 1000 mg/5 mL × 150 mL, dissolved in sodium chloride 0.9% × 2000 mL) were prescribed 4 times per day (rinse and spit for 3 minutes each time), and removal of sharp tooth tubercles was recommended. Three days later the lesions had completely resolved, and everolimus was reintroduced. No recurrence has been reported 19 months since initial presentation.

### Case 2

A 56-year-old woman with breast carcinoma, diagnosed in 1997, developed multiple metastases to the lungs, brain, parencephalis, neck lymph nodes and ribs, first diagnosed in 2005. She underwent surgical excision and radiotherapy for metastases to the neck lymph nodes, cyber knife surgery for rib metastases, and radiotherapy for brain metastases. She was also medicated with 4 mg zoledronic acid (Zometa, Novartis Europharm Ltd, West Sussex, UK) intravenously once every 4 weeks, but it was discontinued in 2007 after she developed mandibular osteonecrosis. Six months before presentation, she was put in a regimen consisting of orally

**Table 1.** Clinical and functional/symptomatic scales of the National Cancer Institute CTCAE v3.0, gastrointestinal adverse event “mucositis/stomatitis”<sup>14</sup>

Grade	1	2	3	4	5
Clinical scale	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
Functional/symptomatic scale	Minimal symptoms, normal diet	Symptomatic but can eat and swallow modified diet	Symptomatic and unable to adequately aliment or hydrate orally	Symptoms associated with life-threatening consequences	Death

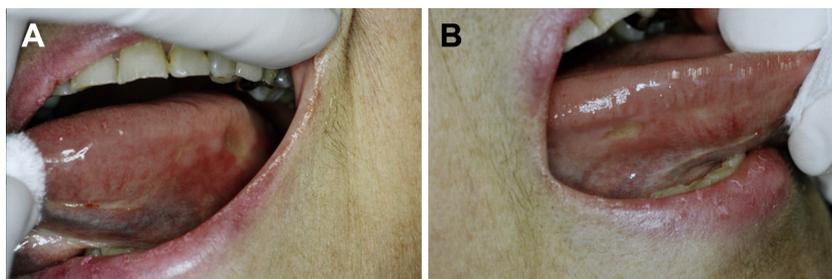


Fig. 2. (Case 2) Two round to oval ulcers on an erythematous base on (A) the left and (B) the right lateral border of the tongue.

administered 10 mg/d everolimus and 25 mg/d exemestane (Aromacin, Pfizer, New York, NY). During the first two 28-day cycles, she had no oral adverse effects and after a 2-month drug holiday, the same regimen was repeated. A month later (approximately 1 month before presentation), she developed “very painful tongue lesions” that became progressively worse, causing difficulties in the consumption of “spicy foods.” She reported daily use of pregabalin and tramadol for the control of bone pain and fluoxetine for depression, and she denied smoking or a history of oral recurrent aphthous ulcerations.

Clinical examination revealed two round-to-oval ulcers on an erythematous base on the left and right lateral borders of the tongue (Figs. 2, A and B), measuring approximately 1 × 0.5 cm and 1 × 0.6 cm, respectively. Due to the history of surgical excision of neck lymph nodes and local radiotherapy, no palpation was attempted. No recent CBC was available. The lesions were considered consistent with mIAS, grade 2 according to CTCAE v3.0 (Table 1),<sup>14</sup> and the same prevention and treatment plans were applied, without modification in the daily dose of everolimus. The patient reported “healing,” with considerable functional improvement in 1 week, but she was consecutively lost to follow-up.

**Case 3**

This case concerns a recurrence of mIAS in a patient first described in another case series.<sup>10</sup> In summary, this 75-year-old woman with breast carcinoma, diagnosed in 2001, developed bone and liver metastases, diagnosed in 2010; in 2011, she was put in a regimen of orally administered 10 mg/d everolimus and 25 mg/d exemestane. Approximately 1 month after the introduction of everolimus, she developed painful oral ulcers, which caused severe difficulty in feeding, and the treatment was discontinued. She was medicated with a

combination of systemic valacyclovir (1 g/d) and metronidazole (1.5 g/d) for 1 week, coupled with topical application of dexamethazone plus miconazole for 2 weeks, which resulted in complete healing. She later resumed everolimus in a dose of 10 mg every other day. She reported that during the next 1.5 months, small ulcers appeared but healed spontaneously in a few days. However, another 1.5 months later, while she was being treated for a tooth abscess, she developed large, very painful ulcers that did not respond to the previous scheme or to “homeopathic drugs,” “laser treatment,” and “local healing agents.” At the time of presentation, she was taking 6 mg ibandronic acid (Bondronat, Roche Registration Ltd, Welwyn Garden City, UK) intravenously once every month for approximately 2 years. She denied smoking and recalled that she, as well as her mother and two sons, were suffering from “recurrent aphthae.”

Clinical examination revealed two irregularly shaped ulcers on the left lateral border of the tongue, covered by a thin pseudomembrane and surrounded by a distinct erythematous halo. The anterior one measured approximately 1.4 × 1.2 cm, and the posterior one 0.8 × 0.6 cm (Figure 3, A). Two smaller ulcers were present on the right side of the mouth floor, measuring approximately 0.5 × 0.2 cm, each (Figure 3, B) and close to the tip of the tongue (<0.1 cm). All lesions were painful on palpation, and she could eat only soft foods. Cervical lymphadenopathy was not present. CBC and biochemical tests revealed mild lymphopenia (24.1%, normal range 25-0%); decreased eosinophils (1.3%, normal range 2%-8%) and hemoglobin (11.9 g/dL, normal range 12.3-15.3 g/dL); increased gamma-glutamyl transpeptidase (GGTP, 41 U/L, normal range 5-36 U/L) and lactate dehydrogenase (LDH, 248 U/L, normal range 135-214 U/L); and positivity for CA125 and CA15-3.

The lesions were considered consistent with mIAS, grade 2 according to CTCAE v3.0 (Table 1)<sup>14</sup>; thus, the same

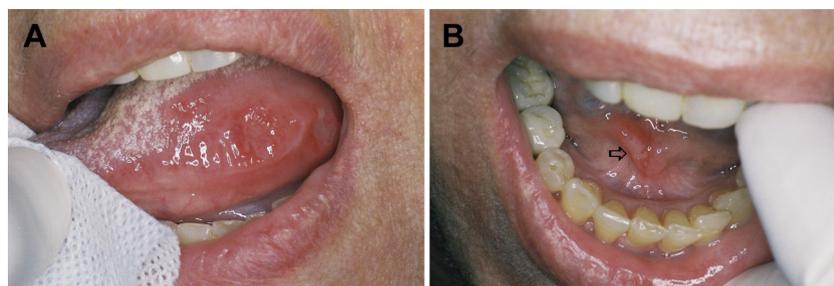


Fig. 3. (Case 3) (A) Two irregularly-shaped ulcers on the left lateral border of the tongue, covered by a thin pseudomembrane and surrounded by a distinct erythematous halo. (B) One smaller ulcer on the right side of the mouth floor (arrow).

**Table II.** Patient characteristics, antineoplastic therapy, mIAS management, and clinical outcome

	Case 1	Case 2	Case 3
Gender/age	Male/69	Female/56	Female/75
Cancer history	Advanced renal cell carcinoma	Breast carcinoma (1997), multiple metastases (since 2007)	Breast carcinoma (2001), bone and liver metastases (since 2010)
Antineoplastic therapy	Nephrectomy (2001) sunitinib malate 75 mg/d/3 mo	Zoledronic acid intravenously (1997-2007), exemestane 25 mg/d/6 mo	Exemestane 25 mg/d/4 mo
mTORI dose	Everolimus 5 mg/d	Everolimus 10 mg/d	Everolimus 10 mg/d/1 mo and 10 mg/2 d/3 mo
Time to onset of pain/oral ulcer	9 d	1 mo	3 mo (last recurrence)
Symptoms	Pain, speech and feeding discomfort	Pain and feeding discomfort with spicy food	Pain, feeding discomfort except only soft food
Clinical presentation of oral ulcers	Ovoid, ulcers, surrounded by a diffuse erythematous area and covered by a thick whitish pseudomembrane on the anterior left buccal mucosa, the right lingual surface of the mandible, and the right lateral border of the tongue	Ulcers on an erythematous base on the left and right lateral border of the tongue	Irregularly-shaped ulcers covered by a thin pseudomembrane and surrounded by a distinct erythematous halo on the left lateral border of the tongue and the right side of the mouth floor
Diagnosis	mIAS (grade 2)*	mIAS (grade 2)*	mIAS (grade 2)*
Management	“Magic mouthwash” oral rinses 4 times/d, temporary discontinuation of everolimus	“Magic mouthwash” oral rinses 4 times/d, no discontinuation of everolimus	“Magic mouthwash” oral rinses 4 times/d, no discontinuation of everolimus
Clinical outcome	Healing (3 d), everolimus reintroduced (5 mg/d), no recurrence 19 mo since presentation	“Healing and considerable functional improvement” (self-reported, 7 d), lost to follow-up	Healing (14 d), small ulcers on the tongue after “self-biting” a few days later; managed in the same way; no recurrence for the next 16 mo

mIAS, mammalian target of rapamycin inhibitors–associated stomatitis; mTORI, mammalian target of rapamycin inhibitors.

\* According both to the clinical and functional/symptomatic of the National Cancer Institute CTCAE v3.0.<sup>14</sup>

prevention and treatment plans were applied, without modification in the daily dose of everolimus. In 2 weeks, the ulcers healed completely, but a few days later, after “self-biting,” the patient developed small ulcers on the tongue, which were managed in the same way. She did not report another recurrence in the subsequent 16 months.

The main clinical characteristics, management, and outcome of the three cases reported here are summarized in Table II.

## DISCUSSION

In the three cases presented here, exposure to everolimus preceded the onset of oral ulcers, although improvement did not necessitate drug withdrawal or reduction in two cases,<sup>15</sup> and the clinical features were consistent with mIAS.<sup>1-3,6,8,9</sup> Differentiation of mIAS from herpetic infection, which is common in immunosuppressed patients, may be difficult, in particular when

mIAS manifests as clustered herpetiform ulcers or as ulcers with irregular borders.<sup>2,6</sup> Presentation of the ulcers on the keratinized mucosa of the palate, gingiva, or tongue dorsum may be suggestive of a viral etiology,<sup>6</sup> but there are rare reports of mIAS with ulcers on those areas.<sup>2,3,9,10</sup> Isolation of herpes simplex virus (HSV) in a tissue culture, as performed in the study by de Oliveira et al.,<sup>2</sup> is the gold standard for virus identification, but the technique is difficult to perform in daily practice, and cytologic smears and serology tests are not sensitive enough to identify HSV infection.<sup>9</sup> A weakness of the current report is that a viral etiology was not ruled out in case 1, where one of the ulcers was located on the keratinized mandibular mucosa. However, a viral etiology was not documented in any previous report of aphthous-like ulcerations in mTORI-treated patients<sup>2,9</sup>; furthermore, virus identification does not exclude mIAS, as it may occur concurrently with HSV infection.<sup>16</sup>

Differential diagnosis of mIAS may, also, include recurrent aphthous stomatitis (RAS), traumatic ulcerations, and neutropenic ulcers. mIAS is clinically identical to RAS,<sup>2,5,6,9,10</sup> and some theories suggest common pathobiologic pathways for both diseases.<sup>1-3,5,6,9</sup> A personal and family history of "recurrent aphthae" was provided by one of our patients, but this could be coincidental, as the prevalence of RAS in the general population is approximately 20%.<sup>17</sup> In addition, such a history is not diagnostic of RAS, as most patients tend to describe any ulcerative oral lesion as "aphthae." mIAS is commonly located on mucosal sites that may be traumatized by the dentition or foodstuffs during mastication.<sup>3</sup> However, a traumatic ulceration would be expected to be solitary and heal after removal of the dentures in case 1 or after a switch to a soft diet that was necessary in all cases. The role of trauma in the development of mIAS should be further investigated, as it is a predisposing factor for RAS.<sup>17</sup> Finally, a typical neutropenic lesion would be expected to manifest as a deep ulcer not surrounded by an erythematous halo, unlike the cases presented herein. In two of our patients for whom a CBC was available, there was bone marrow toxicity that may exist in mIAS,<sup>3,6</sup> but no neutropenia. It should be noted that neutropenia does not exclude a diagnosis of mIAS, as the disease has been reported in patients with neutropenia.<sup>6</sup>

The symptoms in all cases presented here were graded according the National Cancer Institute CTCAE v3.0, considering the gastrointestinal adverse event "mucositis/stomatitis,"<sup>14</sup> as was done in previous case series, as well.<sup>5,9</sup> However, the accuracy of this scale, as well as that of others planned for grading chemotherapy- or radiation-induced mucositis, is questionable.<sup>3,5,9</sup> As in a previous report,<sup>1</sup> all cases presented here were considered to be grade 2, although one of the

patients had been pretreated with sunitinib malate, and the other two were using exemestane concurrently. Previous chemotherapy and concurrent use of other antineoplastic agents or exemestane may have no effect<sup>1,9</sup> or increase<sup>3</sup> the incidence of mIAS, but a combination of mTORI with other antineoplastic drugs is usually associated with more severe symptoms.<sup>3,9</sup> No other oral adverse events of mTORI, that is, xerostomia, taste alteration, or gingival swelling, and gastrointestinal or skin involvement,<sup>5,6,8</sup> were reported by our patients.

The incidence, grade of symptoms, and duration of lesions in mIAS are dose dependent.<sup>2,3</sup> In the study of Ferte et al.,<sup>3</sup> a daily dose of 5 mg was associated with a 57% incidence of mIAS, and a daily dose of 10 mg was associated with a 77% incidence. mIAS was even reported in heart transplant recipients medicated with daily doses of 1.5 mg to 2 mg.<sup>15</sup> A higher dose is also associated with decreased time to onset,<sup>3</sup> which is usually 1 week after the initiation of treatment<sup>1,6</sup> but may vary from a few days to months.<sup>10</sup> Time to onset is subjective, as it is either self-reported by the patient or is estimated from the time the patient asks for medical help; thus, it is influenced by the severity of pain and/or functional disturbance.<sup>9</sup> Two of our patients developed mIAS with reduced doses of 5 mg/d and 10 mg every other day, while the self-reported time to onset ranged from days to 3 months, although in all of them, the severity of symptoms at presentation was similar.

The pathobiology of mIAS is not known. The clinical resemblance of mIAS to RAS<sup>6</sup> focused the research on factors that may be involved in the pathogenesis of the latter. Anemia is common in patients with mIAS,<sup>2</sup> but a role for vitamin B deficiencies was not proved.<sup>11</sup> A decreased CD4 cells count was found in heart transplant recipients treated with everolimus at the time of developing mIAS that tended to increase during its cure,<sup>15</sup> whereas CD4 was suggested to mediate an autoimmune-like inflammatory response to tissue proteins linked with mTORI, in the absence of infection.<sup>5</sup> Trauma, a local predisposing factor in RAS, may also be in effect in mIAS, possibly due to the impaired wound healing caused by the ability of mTORI to suppress angiogenesis and vascular cell proliferation, as well as to induce an increase in glucose levels.<sup>5</sup>

Treatment of mIAS is empirical and usually follows schemes applied in the management of RAS or conventional oral mucositis.<sup>1-3,5,6,8,9</sup> Healing of the ulcers and pain relief is crucial for the continuation of everolimus treatment, as, in a review of 20 studies totaling 1281 patients receiving 10 mg/d everolimus, dose reduction or discontinuation of treatment was necessary in 7.1% and 13.1% of the patients, respectively, due to the development of mIAS.<sup>1</sup> In cases of mIAS grade 2 or 3, a drug holiday was recommended until total healing or improvement to grade 1.<sup>18</sup> Use of corticosteroids

is considered an appropriate therapeutic approach.<sup>2,9,12</sup> In a series of 13 patients treated with everolimus, mIAS improved with topical, intralesional, or systemic corticosteroid therapy; dose reduction was necessitated in 3 patients and drug discontinuation in 1 patient.<sup>2</sup> In 7 female patients with advanced hormone receptor–positive breast cancer, dexamethasone solution with miconazole gel achieved healing of the ulcers in 1 to 2 weeks; temporary discontinuation of everolimus up to 4 weeks was required in 4 cases and dose reduction in 2 cases.<sup>9</sup> In another patient with breast cancer, the same scheme, combined with systemic antivirals and antibiotics, had similar results, and the drug dose was reduced after a 2-week discontinuation.<sup>10</sup>

“Magic mouthwash” offers symptomatic relief in chemotherapy-induced stomatitis and was reported to be effective for pain relief in mIAS.<sup>19-23</sup> However, neither scientific documentation nor adequate empiric evidence is available to justify its use in mIAS<sup>24-26</sup>; thus, other authors do not recommend it.<sup>25,27-29</sup> In our limited experience, the use of a “magic mouthwash” solution 4 times per day offered considerable pain relief, and the ulcers healed in 4 to 15 days, without necessitating dose reduction or discontinuation of everolimus in two cases and without any adverse effect. Although a topical azole is usually included in “magic mouthwash” preparations, we chose to omit it, as there was no evidence of *Candida* infection and its systemic absorption could increase both the serum concentration and the toxic effects of mTORI through cytochrome P450–mediated interaction.<sup>5</sup>

Preventive measures, such as good oral hygiene; diet modification; use of topical analgesic agents; and removal of sodium lauryl sulfate (SLS)–containing toothpastes and debridement agents, such as peroxide-containing mouthwashes, are considered helpful.<sup>5,12,18</sup> Removal of local traumatic precipitants, that is, sharp tooth tubercles, is indicated in patients with RAS<sup>17</sup> and should also be considered in the management of mIAS. However, awareness of health care professionals about this adverse event and education of the patients are of utmost importance, as these may facilitate early diagnosis and management, thus helping the patient avoid lengthy periods of pain and functional disturbance.<sup>5,12</sup>

Recurrence was recorded in 25% of 57 patients, as reported by Ferte et al.,<sup>3</sup> and is more common in patients who have received chemotherapy or a high dose of mTORI. Although in one recent review,<sup>1</sup> no recurrence was found after dose reduction, and subsequent cycles of treatment decreased both the incidence of mIAS and the grade of symptoms. In our case 2, mIAS developed approximately 6 months after initiation of treatment, and in case 3, it recurred at least two times after dose reduction.

In conclusion, mIAS is a common and well-recognized adverse event of everolimus treatment, and its

incidence is expected to rise with the increasing use of everolimus in cancer management. The description of the clinical features, course, and management of more cases in the oral medicine literature will raise awareness about this disease and help in its better characterization, prevention, and control.

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