Panitumumab-associated stomatitis in metastatic colorectal cancer patients: clinical characterization and pathogenic considerations

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Abstract

Purpose: The aim of this study was to report the clinical characterization and management of oral lesions affecting metastatic colorectal cancer (mCRC) patients undergoing panitumumab-containing regimens.

Methods: Electronic medical records of mCRC patients referred to treat mouth sores during the treatment with the EGFR monoclonal antibody – panitumumab – were retrospectively reviewed at two centers. Patients' characterization, clinical profile of oral lesions and management outcomes were documented. Additionally, modifications or discontinuation of the antineoplastic treatment as well as the occurrence of other adverse events (AEs) were analyzed.

Results: A total of 8 patients were included. The oral lesions appeared in a mean time of 9 days (range 7-11 days) following the first cycles. Mean reported pain scores was 6 (range 1-9), causing feeding discomfort. The oral lesions showed a marked aphthous-like appearance in all cases and involved non-keratinized mucosa more likely. Painful atrophic tongue lesions (25%) and angular fissures (37.5%) were also observed. Two patients (25%) required dose reductions or interruptions of the antineoplastic treatment and 1 patient (12,5%) needed discontinuation due to panitumumab-associated stomatitis. Dermatologic AEs were the most prevalent. Clinical improvement was obtained in all patients following management with topical corticosteroid therapy and/or photobiomodulation.

Conclusion: Panitumumab-containing regimes were associated with a particular pattern of oral lesions consistent with stomatitis. Although the lesions responded satisfactorily to corticosteroids and photobiomodulation, modifications or discontinuation of the antineoplastic treatment may eventually occur. Anti-EGFR effects of panitumumab on oral mucosa cells homeostasis seem to play a central role in the pathogenesis of this event.

Introduction

There has been an emergence on the approval and use of several targeted therapies for the treatment of different solid and hematological malignancies [1]. If, on the one hand, it was expected to observe less common systemic adverse events (AEs) when compared to conventional cytotoxic drugs, on the other hand, several other specific AEs and a particular toxicity profile associated with these targeted agents have appeared so far in the clinical routine [2, 3]. Although oral adverse events (OAEs) related to targeted therapies have been reported in the recent literature, it lacks a broad comprehension of the underlying pathogeneses and a consistent clinical characterization of some of these drug-associated reactions [4–7]. As these targeted therapies become more incorporated in oncologic practice, clinicians and patients should be aware of OAEs associated with these drugs, and how to prevent and manage them appropriately.

Oral mucosa injury is a major concern with some therapies that can negatively impact patients' quality of life and may diminish their ability to tolerate cancer treatment, together with a marked increase in the healthcare cost burden and physical and emotional distress [8–12]. Apart from the well-characterized oral mucositis induced by cytotoxic conventional chemotherapy and radiotherapy, Sonis et al. described in 2010 the first cases of an aphthous-like stomatitis affecting cancer patients undergoing mammalian Target of Rapamycin Inhibitors (mTORI) [13]. Although these lesions differed clinically from conventional oral mucositis, resembling more likely recurrent aphthous stomatitis, a significant number of patients eventually required modifications or even discontinuation of the treatment [13–15]. Since that, an increased body of evidence found a high incidence of aphthous-like lesions, named mTORI associated stomatitis (mIAS), in patients undergoing anticancer rapamycin analogs, which have been focus of interdisciplinary care during cancer treatment [14, 16].

Unlike mTORI, the targeted agent panitumumab is an Epithelial Growth Factor Receptor (EGFR) inhibitor recombinant monoclonal antibody fully humanized, which was approved for metastatic colorectal cancer (mCRC) treatment [17]. EGFR, which is expressed in normal and several types of cancer cells, has a pivotal role in promoting cellular proliferation, migration, angiogenesis, and survival by activation of multiple downstream signaling pathways, including the RAS/RAF/MAPK and PI3K/AKT/mTOR pathways [18] (Fig. 1). Therefore, blocking this cell surface protein has granted a significant improvement of clinical outcomes compared to the previous standard therapies, but exclusively in a subset of metastatic colorectal tumors [19]. Although mucositis/stomatitis has been reported in patients undergoing panitumumab for mCRC treatment, no consensus on reporting this phenomenon is available in the literature, and the clinical characterization relies on insufficient anecdotal data [2, 5, 6, 20].

The aim of this study was to characterize the clinical features and management outcomes regarding the OAEs profile of patients treated with panitumumab-containing regimens. Additionally, we discussed the potential interaction between the molecular effects of anti-EGFR drugs and their possible roles in the pathogenesis of oral mucosa changes associated with these targeted therapies.

Material And Methods

A retrospective case record review was conducted at two different dental oncology care facilities in Sao Paulo, Brazil – Instituto do Câncer do Estado de São Paulo (over 6 years) and Hospital Sírio-Libanês (over 1 year). Charts from mCRC patients who underwent panitumumab-containing antineoplastic systemic regimens and were referred to managing mouth sores complaints during the therapy course were assessed.

Data were collected from the electronic medical and dental records using a standardized data collection form and following a data collection guideline to ensure consistency of methodology across both cancer centers. Demographic information, including the patients' characterization, cancer diagnosis profile and antineoplastic treatment information were individually collected. Additionally, electronic records and high-resolution digital photographs were reviewed by an experienced oral medicine specialist (W.G.S). Clinical parameters were assessed, including the time to onset of oral lesions, pain scores (according to a visual analogic scale – VAS), associated oral symptoms, clinical presentation, classification according to size and number of oral lesions, location of the oral lesions, grade (according to the oral mucositis scale of the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 – CTCAE v4.0), management, treatment outcome after management and recurrence rates of the lesions in the subsequent cycles. Dose reduction, delay or interruption in continuing the therapy, and permanent discontinuation of the therapy due to severe toxicities were also reviewed. In addition, other non-oral panitumumab-

associated AEs, including infusion reactions, hematological toxicities, gastrointestinal toxicities, electrolyte imbalances, skin toxicities, among others, were also recorded according to CTCAE scales v4.0. For this analysis, it was recorded only the highest grade of each toxicity during the therapy course when available.

Results

A total of 8 cases of mCRC patients were included in this study. Patients presented a mean age of 54-year-old (37 to 68-year-old) and the oral lesions affected equally both males and females. The patients were diagnosed with metastatic colorectal adenocarcinomas, mostly with usual tubular histologic architecture. All tumors displayed the wild-type (WT) status for *KRAS*, *NRAS* and/or *BRAF* genes, and showed proficient mismatch-repair (pMMR) genes by immunoexpression analysis, except in one case (patient 2). Five patients presented exclusive detectable hepatic metastasis on the start of panitumumab therapy, and 3 patients presented more than 1 sites of metastatic disease. Surgery was previously performed in 5 cases, and radiotherapy or chemoradiotherapy was used in 2 cases. All patients had undergone fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens previously, including modified FLOX (mFLOX), irinotecan as monotherapy and modified FOLFOXIRI (mFOLFOXIRI) protocols. A mean dose of 443,75 mg of panitumumab was administered per patient (ranging from 300 to 600 mg) in an initial 6,0 mg/m^2 protocol. Seven patients underwent panitumumab with concurrent irinotecan in an interval of 14 days (q14w) as 2nd or 3rd line of systemic therapy, and 1 patient underwent mFOLFOXIRI as 1st line therapy (Table 2).

Table 1
Clinical pathologic characterization and antineoplastic treatment information

Patient	Age	Gender	Tumor location	Histologic type (Genomic information)	Sites of metastasis	Previous antineoplastic treatment	Panitumumab initial IV dose	Concurrent CT	Number of cycles	System line therapy
1	56	F	Rectum	Tubulovillous adenocarcinoma (*KRAS* and *NRAS* WT, pMMR)	Hepatic	1- mFLOX 2- RT (5x500cGy) 3- Rectosigmoidectomy 4- Irinotecan monotherapy	400 mg	Irinotecan	7	3rd
2	37	M	Ascending colon	Mucinous adenocarcinoma (*KRAS* and *NRAS* WT, dMMR)	Hepatic and non-regional lymph nodes	1- mFLOX 2- Roswell Park 5-FU maintenance CT regimen 3- re-exposure to mFLOX 4- Irinotecan monotherapy	600 mg	Irinotecan	3	3rd
3	63	F	Sigmoid colon	Tubular adenocarcinoma (*KRAS* and *NRAS* WT, pMMR)	Hepatic	1- Right Hemicolectomy for AIO 2- mFLOX	300 mg	Irinotecan	7	2nd
4	50	F	Sigmoid colon	Tubular adenocarcinoma (*KRAS* and *NRAS* WT, pMMR)	Hepatic	1- Sigmoidectomy for AIO 2- mFLOX 3- Roswell Park 5-FU maintenance CT regimen 4- re-exposure to mFLOX	300 mg	Irinotecan	15	2nd
5	66	M	Rectum	Tubular adenocarcinoma (*KRAS* and *NRAS* WT, MMR status NA)	Hepatic	1- mFLOX + Palliative RT 2- Irinotecan monotherapy	500 mg	Irinotecan	11	3rd
6	53	F	Rectum	Tubular adenocarcinoma (*KRAS* and *NRAS* WT, pMMR)	Hepatic	1- Retosignoidectomy 2- mFLOX 3- Irinotecan monotherapy	400 mg	Irinotecan	11[α]	3rd
7	68	M	Rectum	Tubular adenocarcinoma (*KRAS* and *NRAS* WT, pMMR)	Pelvic, lymph nodes and bone metastasis (L5 vertebra)	1- Neoadjuvant CRT 2-Abdmonioperineal rectum amputation 3- Participated in a clinical trial (observational arm) 3- mFLOX 4- Irinotecan monotherapy	450 mg	Irinotecan	5[β]	3rd

Abbreviations: IV, intravenous; CT, chemotherapy; WT, wild-type; pMMR, proficient mismatch-repair genes; dMMR, deficient mismatch-repair genes; NA, not available; mFLOX, modified FLOX regimen, RT, radiotherapy; 5-FU, 5-fluorouracil; AIO, acute intestinal obstruction, NA, not available, CRT, chemoradiotherapy; mFOLFOXIRI, modified FOLFOXIRI.

[α] Panitumumab was changed by cetuximab 500 mg/m^2 after the 5th cycle of the treatment.

[β] Patient 7 underwent one rechallenge cycle of panitumumab with concurrent irinotecan after interrupt the treatment due to lack of compliance.

[γ] Panitumumab was added only to the 3rd and 4th cycles of the treatment.

Patient	Age	Gender	Tumor location	Histologic type (Genomic information)	Sites of metastasis	Previous antineoplastic treatment	Panitumumab initial IV dose	Concurrent CT	Number of cycles	System line therapy
8	43	M	Rectosigmoid junction	Adenocarcinoma (*KRAS*, *NRAS* and *BRAF* WT, and pMMR)	Hepatic, regional and non-regional lymph nodes, thyroid gland, lung and multiple bone sites	1- mFOLFOXIRI	600 mg	5-FU Oxaliplatine Irinotecan	8[γ]	1st

Abbreviations: IV, intravenous; CT, chemotherapy; WT, wild-type; pMMR, proficient mismatch-repair genes; dMMR, deficient mismatch-repair genes; NA, not available; mFLOX, modified FLOX regimen, RT, radiotherapy; 5-FU, 5-fluorouracil; AIO, acute intestinal obstruction, NA, not available, CRT, chemoradiotherapy; mFOLFOXIRI, modified FOLFOXIRI.

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[γ] Panitumumab was added only to the 3rd and 4th cycles of the treatment.

Table 2
Panitumumab-associated stomatitis clinical characterization, management, and clinical outcome

Patient	Time of onset (days)	Highest pain score (VAS)	Oral symptoms	Clinical features	Classification according to size/shape and number of oral lesions	Location of the lesions	Initial grade/highest grade (CTCAE v4.0)	Management	Clinical outcome	Recurrence of oral lesions
1	8	7	Pain Feeding discomfort	Aphthous-like ulcers	Minor (n = 4) Herpetiform (n = 4)	Upper lip mucosa Lower lip mucosa Ventrolateral tongue area Buccal mucosa	2/2	- Sodium bicarbonate mouth wash (S&Sp) - Alumni Hydroxide - Topical anesthetic - Acetonide triamcinolone - PBM (n = 5)	CR	Y
2	7	NR	Pain Feeding discomfort	Aphthous-like ulcers Well-demarked atrophic erythematous lesions Angular cheilitis	Minor (n = 2) Atrophic (n = 2) Angular fissures (unilateral)	Ventrolateral tongue area Tip of tongue	2/2	- PBM (n = 1)	CR	Y
3	11	1	Pain Feeding discomfort	Isolated aphthous-like ulcer in healing process Angular cheilitis	Minor (n = 1) Angular fissures (bilateral)	Ventrolateral tongue area	2/2	Not performed	CR	N
4	10	5	Pain Feeding discomfort	Aphthous-like ulcers	Minor (n = 9)	Upper lip mucosa Lower lip mucosa Buccal mucosa Ventrolateral tongue area Floor of mouth Gingiva	2/2	- Bicarbonate mouth wash (S&Sp) - Artificial saliva - PBM (n = 5) - Topical clobetasol propionate 0,05%	CR	N
5	10	5	Pain Feeding discomfort	Aphthous-like ulcers and Well-demarked atrophic erythematous lesions	Minor (n = 1) Herpetiform (n = 1) Atrophic (n = 2)	Ventrolateral tongue area Soft palate	2/2	- Self-use of propolis - Topical clobetasol propionate 0,05% - Prednisone 40mg	CR	Y
6	7	5	Pain Feeding discomfort Speaking discomfort	Aphthous-like ulcers Well-demarked atrophic erythematous lesions	Minor (n = 4)	Alveolar mucosa at mandibular torus Tip of tongue Ventrolateral tongue area Soft palate	2/2	- Bicarbonate mouth wash (S&Sp) - Topical clobetasol propionate 0,05%	CR	Y

Abbreviations: VAS, visual analogue scale; NR, not reported; CTCAE v4.0, Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; S&S, swish and speech; PBM, photobiomodulation; PO, per oral; IV, intravenous; CR, complete resolved; Y, yes; N, no.

Patient	Time of onset (days)	Highest pain score (VAS)	Oral symptoms	Clinical features	Classification according to size/shape and number of oral lesions	Location of the lesions	Initial grade/highest grade (CTCAE v4.0)	Management	Clinical outcome	Recurrence of oral lesions
7	11	9	Pain Feeding limitation	Aphthous-like ulcers Angular cheilitis Herpetic lesions	Minor (n = 2) Angular fissures (bilateral) Herpetic (multiple and coalescent)	Lower lip mucosa Buccal mucosa Soft palate Alveolar bridge Dorsum of the tongue	3/3	- PBM (n = 5) - Acyclovir 400mg PO	CR	N
8	NR	8	Pain Feeding limitation	Aphthous-like ulcers Confluent ulceration	Minor (n = 3) Major (n = 1)	Floor of mouth Ventrolateral tongue area Soft palate Lower lip mucosa	2/4	- PBM (n = 5) - Valacyclovir 200mg IV	CR	Y

Abbreviations: VAS, visual analogue scale; NR, not reported; CTCAE v4.0, Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; S&S, swish and speech; PBM, photobiomodulation; PO, per oral; IV, intravenous; CR, complete resolved; Y, yes; N, no.

The oral lesions appeared in a mean time of 9 days (range 7–11 days) in 6 patients (75%) following the first cycles (1st or 2nd) of panitumumab-containing regimes. However, one case occurred initially following the 4th cycle of panitumumab plus irinotecan (patient 4), and another case occurred after a rechallenge of the therapy (patient 7) due to previous lack of treatment compliance. All patients complained of pain and feeding discomfort, including 2 of them with significant limited oral intake. Median pain score was 6 (range 1–9) across the patients'-reported symptoms analysis. All the patients presented small round/ovoid-shaped shallow ulcerations covered by a gray/white pseudomembrane and associated with a surrounding intense erythematous halo, which showed a markedly aphthous-like appearance. It usually affected the moveable non-keratinized mucosa of multiple oral sites, more likely in the ventrolateral border of tongue (25%), lips (21.4%), soft palate (14.3%) and buccal mucosa (10.7%). Minor aphthous-like lesions (≤ 1 cm) were observed in all cases with a mean of 3 lesions per patients (range, 1–9 lesions). Major aphthous phenotype (> 1 cm) were encountered in 1 patient, and herpetiform aphthous lesions were found in 2 cases. Atrophic and erythematous well-demarcated painful tongue lesions, which resembled symptomatic benign erythematous stomatitis, were observed in 2 patients. Angular cheilitis with unilateral or bilateral fissures on the corner of lips was also present in 3 cases as well (Fig. 2). One patient (patient 7) presented coalescent painful shallow and irregular ulcerations affecting keratinized mucosa, showing a marked herpetic appearance in the dorsum of the tongue, lips and palate with some typical aphthous-like lesions in the background affecting non-keratinized mucosa. Smear samples from only this former case showed conspicuous cytopathic viral inclusions in epithelial cells suggesting herpes simplex virus (HSV) superinfection. At the initial presentation, all cases were grade 2 according to CTCAE v.4.0, except one case grade 3 (patient 6).

Patients were variably managed with a combination of basic oral care, palliative medications, topical and systemic corticosteroid therapy, as well as intraoral photobiomodulation (PBM) with curative intent. Palliative treatments included topical anesthetics, coating agents, oral lubricants, saline rinses, and analgesics. Basic oral care, which included education, oral hygiene instructions, and alcohol-free chlorhexidine 0.12% mouth wash prescriptions, was conducted in all cases following initial evaluation. Palliative treatment was provided for 7 (87.5%) patients, including lidocaine 2% jelly or tetracaine spray (37,5%), alumni hydroxide (12,5%), swish and speech sodium bicarbonate mouth washes (50%), and artificial saliva (25%). Treatment with topical corticosteroids was performed in 4 (50%) of the patients with topical clobetasol propionate 0.05% locally applied to the lesions for 1 minute 1–3 times daily for 2–3 weeks. One case was also managed with acetonide triamcinolone before referral to dental evaluation. Intraoral PBM was used to treat 4 patients (50%), and a curative protocol (dual wavelength 660/808 nm, 0.1W, 2–4 J per point, 20–40 seconds per point, 22.2–44.4 J/cm^2) was used with a median of 4 applications once a day (ranging from 1 to 5). One patient (patient 5) was concomitantly treated with topical corticosteroid and systemic prednisone 40mg daily for 7 days. Patient 7 was additionally treated for HSV oral infection with acyclovir in therapeutics doses 400mg every 6 hours for 7 days concomitantly to palliative treatment, analgesics and intraoral PBM. Patient 8 was managed with valacyclovir 200mg daily for 7 days due to HSV infection suspicion which was not confirmed by protein chain reaction test. Clinical improvement was observed in all cases managed and represented either symptoms relief or mucosal healing. Complete resolution of oral lesions was observed in all cases in a mean time of 1 week (1–3 weeks) following the initial oral management.

Recurrences after primary treatment of panitumumab-associated stomatitis occurred in 5 cases. The cases that recurred maintained as same severity grade or decreased, except in the case of patient 8 (Table 2). This patient (patient 8) developed a severe grade 4 stomatitis and skin acneiform rash when tested positive for SARS-CoV-2 with mild pulmonary involvement and flu-like symptoms, needing hospitalization. The recurrences were managed with continuous palliative treatment in all cases. Either topical clobetasol 0.05% applications or dexamethasone 0.1mg/mL swish and speech mouth washes 2–3 daily were used after recurrence in subsequent cycles. Two patients were systemically managed with prednisone and methylprednisolone 40mg daily for 5–7 days, respectively, due to severe skin and oral AEs in the following cycles. PBM was performed in 3 recurring cases.

Dose reductions were performed in 6 cases (75%) during the treatment course, ranging from 15–33% less of the initial dose. Out of these 6 cases, 4 involved dose reductions of both chemotherapeutics and panitumumab, and 2 cases involved chemotherapy or panitumumab reduction alone. Dose reductions and treatments delays or interruptions were related to panitumumab-associated stomatitis in 2 cases (25%). Permanent discontinuation of the treatment due

toxicity was needed in 2 cases (25%), nonetheless only in 1 case (12.5%) panitumumab-containing treatment was interrupted due to severe stomatitis and acneiform rash grade 4 (12.5%). In this case, the patient was not able to maintain oral intake and parenteral nutrition was started until patient could eat soft food appropriately. In another case, the therapy was discontinued due to cumulative hematological toxicity (anemia and neutropenia grade 3), diarrhea and fatigue grade 2. The other patients continued the therapy until detectable disease progression was confirmed or patients presented significant worsening of the performance status. For logistic reasons, the patient 6 had to change the monoclonal antibody panitumumab by cetuximab after the 5th cycle.

The patients experienced other common AEs associated to panitumamab-cointaing regimes, most frequently dermatologic toxicities. Anemia, neutropenia, and acneiform skin rash were the only toxicities grade 3–4 observed. The acneiform skin rash represented the most common AE (100%) in the current cases (Fig. 3), followed by fatigue (87.5%), nausea (87.5%), and diarrhea (75%) (Table 3). Sporadic cases of trichomegaly, onycholysis, skin hyperpigmentation, pyogenic granuloma, bleeding events, xerophthalmy, skin abscess, palmar-plantar erythrodysaesthesia, and constipation were also reported.

Table 3
Non-oral adverse events associated with panitumumab containing-regimes

Adverse Events	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Hematological disorders	+ / G2	- / -	+ / G3	+ / G2	- / -	- / -	- / -	+ / G2
Anemia	- / -	- / -	+ / G3	+ / G2[β]	- / -	+ / G2	- / -	- / -
Neutropenia	+ / G1	+ / G2	+ / NR	- / -	+ /G1	+ / G1	+ / G1	- / -
Nausea								
Gastrointestinal disorders	- / -	+ / NR	+ / NR	- / -	- / -	- / -	- / -	- / -
Vomiting	+ / G2	+ / G1	+ / G2	- / -	- / -	+ / G1	+ / G2	+ / G1
Diarrhea								
Skin disorders	+ / G3	+ / G2	+ / G1	+ / G2	+ / G3	+ / G3	+ / G1	+ / G4
Acneiform skin rash	+ / G1	- / -	+ / G2	+ / G1	- / -	- / -	- / -	- / -
Dry skin	+ / G2	+ / NR	- / -	- / -	- / -	+ / NR	- / -	- / -
Skin Fissures	- / -	- / -	- / -	- / -	+ / NR	+ / NR	- / -	- / -
Pruritus	+ / NR	+ / NR	- / -	- / -	- / -	+ / G1	- / -	- / -
Paronychia	+ / NR	- / -	+ / NR	+ / NR	- / -	- / -	+ / G2	- / -
Alopecia								
Electrolyte's imbalances	+ / NR	- / -	+ / G1	+ / G1	+ / G2	+ / G1	+ / G2	+ / NR
Hypomagnesemia								
Others	- / -	+ / NR[α]	- / -	- / -	- / -	- / -	- / -	- / -
Infusion reaction	+ / NR	- / -	+ / G1	+ / G1	+ / G2	+ / G1	+ / G2	+ / NR
Fatigue	- / -	- / -	+ / NR	+ / G1	- / -	- / -	- / -	- / -
Peripheral neuropath								

G, grade (according to CTACCE v 4.0); NR, not reported.

[α] Cholinergic reaction immediately after irinotecan infusion.

[β] Neutropenia with a subfebrile episode.

Discussion

Contemporary, CRC is considered a molecularly heterogeneous malignancy characterized by several genomic and epigenomic alterations used to assess prognostic information and to guide the best treatment approach [21, 22]. Targeted therapies, including anti-EGFR panitumumab and cetuximab, have been introduced in the treatment of mCRC at selective settings [22–28]. Although OAEs related to panitumumab have been reported in mCRC patients, it lacked well-documented descriptions of these cases as well as an analysis of effectiveness on the management of these events [2, 5, 6]. To the best of our knowledge, we present the first study documenting the clinical patterns of aphthous-like and atrophic tongue lesions associated with panitumumab-containing regimens and the outcomes following our experience in treating this condition.

A systematic review that analyzed the risk of grade ≥ 3 mucositis in CRC patients treated with anti-EGFR regimens found that the risk ratio was 3.44, particularly for patients undergoing panitumumab-containing regimes [29]. Besides the apparent low risk of severe cases (grade ≥ 3) of mucositis/stomatitis for patients undergoing panitumumab in accordance with our findings, the impact on patients' quality of life might be underestimated, considering the frequency of modifications needs on ongoing treatments and patient-reported symptoms described in this series. Additionally, there has been no standard characterization of this phenomenon in the available trials, and experienced oral clinicians are not usually involved in these studies. In a brief review of studies regarding panitumumab safety analysis, a broad range of terms such as mucositis, stomatitis, mucosal inflammation, among other unspecific terms, were

included to reporting oral mucosa changes [22, 25–29], which may compromise the accuracy in systematically determine whether they represented conventional oral mucositis or were in the medication-associated stomatitis spectrum. The marked aphthous-like appearance and tongue atrophic lesions observed in our study suggest that these cases represent more likely stomatitis than genuine oral mucositis as the cases described by Sonis et al. previously [13]. Therefore, we believe that the term panitumumab-associated stomatitis may better represent the clinical profile of this oral toxicity.

Most commonly, anti-EGFR targeted therapies have been associated with a significantly increased risk of skin toxicity, affecting even 90% of the patients undergoing these drugs [30–33]. Dermatologic changes associated with panitumumab include a broad spectrum that may involve cutaneous and skin adnexal disorders [32, 33]. The patients analyzed in the current study presented several dermatologic toxicities during the treatment course. Acneiform rash in the face and/or trunk was present in all our patients attending concomitantly to oral lesions. It frequently represented an early event of clinical relevance in the toxicity profile and preceded the oral lesions. The close biological and molecular signature of mucosal and epidermal keratinocytes may explain this specific profile which reflects mainly disturbances of EGFR inhibition. Interestingly, severity and early timing onset of skin toxicity has been associated with better survival outcomes, being a surrogate marker of a better panitumumab clinical response [31, 33]. Considering the limited number of cases presented herein, it is not already possible to assume the same conclusions regarding the oral toxicity profile.

EGFR activation is involved in several physiologic cellular processes as differentiation, proliferation, cell migration, and blood flow changes, essential for mucocutaneous homeostasis and tissue repair. EGF signaling is considered a key regulator of gastrointestinal tract mucosal barrier integrity [34], and disturbances in this pathway are associated with increased epithelium permeability and wound healing impairment [35, 36]. EGF that is constitutively produced in salivary fluid has been investigated in the pathophysiology of recurrent aphthous stomatitis, even though some results were controversial [37, 38]. Gu et al. [39] suggested that the decrease in salivary EGF in the remission interval of patients with recurrent aphthous stomatitis would be related to the ulcer initiation phase, and EGFR activation may be crucial to the resolution of the aphthous lesions. However, another study by Rezae et al. [40] did not found differences in salivary EGF levels between affected patients and controls. Recurrent aphthous stomatitis, which closely resembles the oral lesions observed herein, is considered an immunologically driven multifactorial disease of unknown etiology [41, 42] and the current findings regarding EGF-EGFR disturbances may add a valuable information to better understand its intriguing and complex pathogenesis.

Although the underlying pathogenesis of panitumumab-associated stomatitis remains unclear at this point, we hypothesize that the inhibition of EGFR may elicit a particular inflammatory and apoptotic signaling to the oral mucosa cells, predisposing to epithelial damage and disruption of the mucosal barrier, which ultimately can result in ulceration and pain in a similar way to recurrent RAS lesions. Additionally, the complex EGFR inhibitory effects on the immune system response and the decrease in the immunosurveillance to oral pathogens can also be involved in this process. Pathogens such as HSV and the new coronavirus (SARS-CoV-2) were associated with increased severity in our cases.

Another point is that the combination of panitumumab to chemotherapy and the type of concurrent drug may contribute to the compromise of the protective factors and regenerative capacity of the oral mucosa. Notwithstanding, most of our cases were previously treated with irinotecan alone before starting the combined therapy with panitumumab in a subsequent line, and no evidence of reported oral lesions was retrieved in our analysis, which point out to the key role of the anti-EGFR effects. In addition, the clinical presentation of our cases was similar regardless of concurrent chemotherapeutic scheme or treatment line, but the treatment combinations did not vary significantly across the patients. Interestingly, anti-EGFR tyrosine kinases inhibitors used to treat advanced non-small-cell lung cancer have been attended to a similar risk of stomatitis [43, 44], which corroborate our idea that EGFR blockage effects seem pivotal on pathogenic events following this OAE.

Although delaying on treatment sequence, interruptions or even discontinuation due to oral lesions represented few cases, our results emphasize the emerging need of guided oral care protocols for mCRC patients undergoing anti-EGFR targeted drugs. Despite the small sample size, the herein characterized panitumumab-associated stomatitis responded well either to topical corticosteroids or to PBM alone or in combination, which improved the healing of impaired EGFR-signaling oral mucosa cells. We also believe that basic oral care and oral palliative treatment may be incorporated to the routine of treatment of patients that develop these mouth sores. Even though PBM proved to be effective as well, the compliance to daily applications and the variability of possible settings may be taken in count. Preventive measures including light-based approaches and systemic or topical corticosteroids seem to be encouraging.

Based on the retrospective nature of our study, we highlight some limitations of our findings. The small number of patients by the convenience of the sample, the lack of heterogeneity between the treatment protocols which did not include patients undergoing panitumumab as monotherapy, and the variability in the management of this condition that was not uniform across the patients and during the patients' follow-up are some examples that would be overcome in the future. Prospective studies, including clinical trials, will be necessary to design preventive strategies and test curative protocols in managing panitumumab-associated stomatitis more accurately.

In conclusion, panitumumab-containing regimes were associated with a particular pattern of painful aphthous-like and atrophic tongue lesions that were accompanied by a marked acneiform cutaneous rash following the beginning of the therapy as well as several other AEs. The lesions were similar to recurrent aphthous stomatitis, and it was eventually able to cause modifications or discontinuation of the antineoplastic treatment schedule like the previously reported mIAS. Our preliminary results found that topical corticosteroids as clobetasol propionate 0.05% and/or PBM were effective on treating panitumumab-associated stomatitis. The anti-EGFR effects of panitumumab on oral mucosa cells homeostasis seem to play a central role in the pathogenesis of this poorly understood condition. We strongly believe that preventive measures, early recognition by trained clinicians, and the correct management of this OAE may be helpful to improve the compliance of patients to the antineoplastic treatment and maintain their quality of life at adequate levels during the treatment course of panitumumab.

Declarations

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Consent to participate: Not applicable.

Consent to publish: Informed consent was obtained from the patients to the use of clinical images.

References

1. Joo WD, Visintin I, Mor, G (2013) Targeted cancer therapy – Are the days of systemic chemotherapy numbered? Maturitas 76(4):308–314. doi: 10.1016/j.maturitas.2013.09.008.
2. Lacouture M, Sibaud V (2018) Toxic Side Effects of Targeted Therapies and Immunotherapies Affecting the Skin, Oral Mucosa, Hair, and Nails. Am J Clin Dermatol 19(Suppl 1):31–39. doi: 10.1007/s40257-018-0384-3.
3. Anders CK, LeBoeuf NR, Bashoura L, Faiz SA, Shariff AI, Thomas A (2020) What's the Price? Toxicities of Targeted Therapies in Breast Cancer Care. Am Soc Clin Oncol Educ Book 40:55–70. doi: 10.1200/EDBK_279465.
4. Vigarios E, Epstein JB, Sibaud V (2017) Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. Support Care Cancer 25(5):1713–1739. doi: 10.1007/s00520-017-3629-4.
5. Watters AL, Epstein JB, Agulnik M (2011) Oral complications of targeted cancer therapies: a narrative literature review. Oral Oncol 47(6):441–8. doi: 10.1016/j.oraloncology.2011.03.028.
6. Carrozzo M, Eriksen JG, Bensadoun RJ, Boers-Doets CB, Lalla RV, Peterson DE (2019) Oral Mucosal Injury Caused by Targeted Cancer Therapies. J Natl Cancer Inst Monogr 2019(53):lgz012. doi: 10.1093/jncimonographs/lgz012.
7. Yuan A, Woo SB. Adverse drug events in the oral cavity (2015) Oral Surg Oral Med Oral Pathol Oral Radiol 119(1):35–47. doi: 10.1016/j.oooo.2014.09.009.
8. Kauark-Fontes E, Rodrigues-Oliveira L, Epstein JB, Faria KM, Araújo ALD, Gueiros LAM, Migliorati CA, Salloum RG, Burton P, Carroll J, Lopes MA, Alves CGB, Palmier NR, Prado-Ribeiro AC, Brandão TB, Santos-Silva AR (2021) Cost-effectiveness of photobiomodulation therapy for the prevention and management of cancer treatment toxicities: a systematic review. Support Care Cancer 29(6):2875–2884. doi: 10.1007/s00520-020-05949-1.
9. Epstein JB, Thariat J, Bensadoun RJ, Barasch A, Murphy BA, Kolnick L, Popplewell L, Maghami E (2012) Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. CA Cancer J Clin 62(6):400–22. doi: 10.3322/caac.21157.
10. Lalla RV, Saunders DP, Peterson DE. Chemotherapy or radiation-induced oral mucositis (2014) Dent Clin North Am 58(2):341–349. doi: 10.1016/j.cden.2013.12.005.
11. Jehn P, Stier R, Tavassol F, Dittmann J, Zimmerer R, Gellrich NC, Krüskemper G, Spalthoff S (2019) Physical and Psychological Impairments Associated with Mucositis after Oral Cancer Treatment and Their Impact on Quality of Life. Oncol Res Treat 42(6):342–349. doi: 10.1159/000499720.
12. Rosenthal DI. Consequences of mucositis-induced treatment breaks and dose reductions on head and neck cancer treatment outcomes (2007) J Support Oncol 5(9 Suppl 4):23–31.
13. Sonis S, Treister N, Chawla S, Demetri G, Haluska F (2010) Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. Cancer 116(1):210-215z.
14. Lo Muzio L, Arena C, Troiano G, Villa A (2018) Oral stomatitis and mTOR inhibitors: A review of current evidence in 20,915 patients. Oral Dis 24(1–2):144–171. doi: 10.1111/odi.12795.
15. Shameem R, Lacouture M, Wu S (2015) Incidence and risk of high-grade stomatitis with mTOR inhibitors in cancer patients. Cancer Invest 33(3):70–77. doi: 10.3109/07357907.2014.1001893.
16. Nicolatou-Galitis O, Nikolaidi A, Athanassiadis I, Papadopoulou E, Sonis S (2013) Oral ulcers in patients with advanced breast cancer receiving everolimus: a case series report on clinical presentation and management. Oral Surg Oral Med Oral Pathol Oral Radiol 116(2):e110-116. doi: 10.1016/j.oooo.2013.02.022.
17. Hutchinson, L (2010) Panitumumab improves PFS in mCRC with wild-type KRAS. Nat Rev Clin Oncol 7(12):672. doi: 10.1038/nrclinonc.2010.
18. Markowitz SD, Bertagnolli MM (2009) Molecular origins of cancer: Molecular basis of colorectal cancer. N Engl J Med 17;361(25):2449–2460. doi: 10.1056/NEJMra0804588.

19. Saif MW (2010) Colorectal cancer in review: the role of the EGFR pathway. Expert Opin Investig Drugs 19(3):357–369. doi: 10.1517/13543781003593962.
20. Sibaud V, Boralevi F, Vigarios E, Fricain JC (2014) Toxicité endobuccale des thérapies ciblées anticancéreuses [Oral toxicity of targeted anticancer therapies]. Ann Dermatol Venereol 141(5):354–363. French. doi: 10.1016/j.annder.2014.03.009.
21. Ewing I, Hurley JJ, Josephides E, Millar A (2014) The molecular genetics of colorectal cancer. Frontline Gastroenterol 5(1):26–30. doi: 10.1136/flgastro-2013-100329.
22. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, Canon JL, Van Laethem JL, Maurel J, Richardson G, Wolf M, Amado RG (2007) Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 25(13):1658–1664. doi: 10.1200/JCO.2006.08.1620.
23. Hoff PM, Ellis LM. Targeted therapy trials: approval strategies, target validation, or helping patients? (2007) J Clin Oncol25(13):1639-41. doi: 10.1200/JCO.2006.09.8384.
24. Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360(14):1408–1417. doi: 10.1056/NEJMoa0805019.
25. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Oliner KS, Wolf M, Gansert J (2010) Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 28(31):4697–46705. doi: 10.1200/JCO.2009.27.4860.
26. Price TJ, Peeters M, Kim TW, Li J, Cascinu S, Ruff P, Suresh AS, Thomas A, Tjulandin S, Zhang K, Murugappan S, Sidhu R (2014) Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol 15(6):569–579. doi: 10.1016/S1470-2045(14)70118-4.
27. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Oliner KS, Tian Y, Xu F, Sidhu R (2014) Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 25(7):1346–1355. doi: 10.1093/annonc/mdu141.
28. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, André T, Chan E, Lordick F, Punt CJ, Strickland AH, Wilson G, Ciuleanu TE, Roman L, Van Cutsem E, Tian Y, Sidhu R (2014) Final results from a randomized phase 3 study of FOLFIRI {+/-} panitumumab for second-line treatment of metastatic colorectal cancer. Ann Oncol 25(1):107–116. doi: 10.1093/annonc/mdt523.
29. Miroddi M, Sterrantino C, Simonelli I, Ciminata G, Phillips RS, Calapai G (2015) Risk of grade 3–4 diarrhea and mucositis in colorectal cancer patients receiving anti-EGFR monoclonal antibodies regimens: A meta-analysis of 18 randomized controlled clinical trials. Crit Rev Oncol Hematol 96(2):355–371. doi: 10.1016/j.critrevonc.2015.06.004.
30. Lacouture ME, Melosky BL (2007) Cutaneous reactions to anticancer agents targeting the epidermal growth factor receptor: a dermatology-oncology perspective. Skin Therapy Lett 12(6):1–5.
31. Lacouture ME, Mitchell EP, Piperdi B, Pillai MV, Shearer H, Iannotti N, Xu F, Yassine M (2010) Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-Emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 28(8):1351–1357. doi: 10.1200/JCO.2008.21.7828.
32. Belum VR, Cercek A, Sanz-Motilva V, Lacouture ME (2013) Dermatologic adverse events to targeted therapies in lower GI cancers: clinical presentation and management. Curr Treat Options Oncol 14(3):389–404. doi: 10.1007/s11864-013-0254-4.
33. Lacouture ME, Anadkat M, Jatoi A, Garawin T, Bohac C, Mitchell E (2018) Dermatologic Toxicity Occurring During Anti-EGFR Monoclonal Inhibitor Therapy in Patients With Metastatic Colorectal Cancer: A Systematic Review. Clin Colorectal Cancer 17(2):85–96. doi: 10.1016/j.clcc.2017.12.004.
34. Tang X, Liu H, Yang S, Li Z, Zhong J, Fang R (2016) Epidermal Growth Factor and Intestinal Barrier Function. Mediators Inflamm 2016:1927348. doi: 10.1155/2016/1927348.
35. Bandara M, MacNaughton WK (2021) Protease-activated receptor-2 activation enhances epithelial wound healing via epidermal growth factor receptor. Tissue Barriers 11:1968763. doi: 10.1080/21688370.2021.1968763.
36. Suzuki T, Seth A, Rao R (2008) Role of phospholipase Cgamma-induced activation of protein kinase Cepsilon (PKCepsilon) and PKCbetaI in epidermal growth factor-mediated protection of tight junctions from acetaldehyde in Caco-2 cell monolayers. J Biol Chem 283(6):3574–3583. doi: 10.1074/jbc.M709141200.
37. Epstein JB, Gorsky M, Guglietta A, Le N, Sonis ST (2000) The correlation between epidermal growth factor levels in saliva and the severity of oral mucositis during oropharyngeal radiation therapy. Cancer 89(11):2258–2265. doi: 10.1002/1097-0142(20001201)89:11<2258::aid-cncr14>3.0.co;2-z.
38. Adişen E, Aral A, Aybay C, Gürer MA (2008) Salivary epidermal growth factor levels in Behçet's disease and recurrent aphthous stomatitis. Dermatology 217(3):235–240. doi: 10.1159/000148250.
39. Gu Y, Zhang G, Lin M (2008) [Quantity research on epidermal growth factor in saliva and epidermal growth factor receptor in biopsy samples of recurrent aphthous ulcer patients]. Hua Xi Kou Qiang Yi Xue Za Zhi 26(1):36–39. Chinese.
40. Rezaei F, Hosseini E, Rezaei F (2019) Comparison of salivary epidermal growth factor in patients with recurrent aphthous stomatitis, smokers, and healthy individuals. J Family Med Prim Care 8(8):2587–2591. doi: 10.4103/jfmpc.jfmpc_397_19.
41. Scully C, Porter S (2008) Oral mucosal disease: recurrent aphthous stomatitis. Br J Oral Maxillofac Surg 46(3):198–206. doi: 10.1016/j.bjoms.2007.07.201.

42. Slebioda Z, Szponar E, Kowalska A (2014) Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review. Arch Immunol Ther Exp (Warsz) 62(3):205–15. doi: 10.1007/s00005-013-0261-y.
43. Zhou JY, Liu SY, Wu YL (2020) Safety of EGFR-TKIs for EGFR mutation-positive non-small cell lung cancer. Expert Opin Drug Saf 19(5):589–599. doi: 10.1080/14740338.2020.1753697.
44. Aw DC, Tan EH, Chin TM, Lim HL, Lee HY, Soo RA (2018) Management of epidermal growth factor receptor tyrosine kinase inhibitor-related cutaneous and gastrointestinal toxicities. Asia Pac J Clin Oncol 14(1):23–31. doi: 10.1111/ajco.12687.

Figures

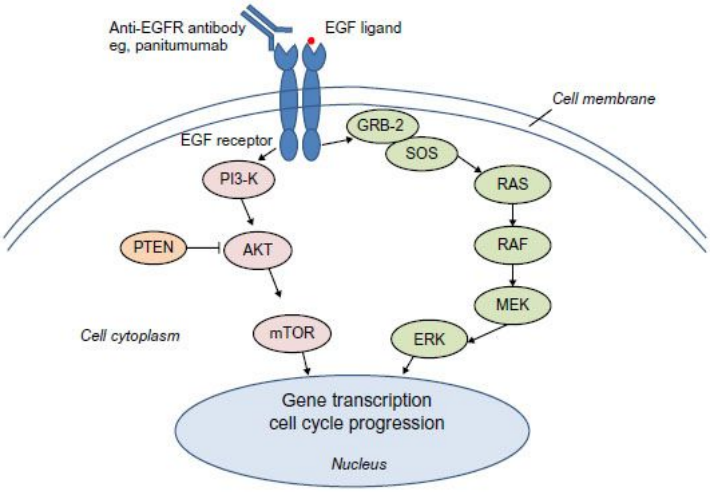

Figure 1

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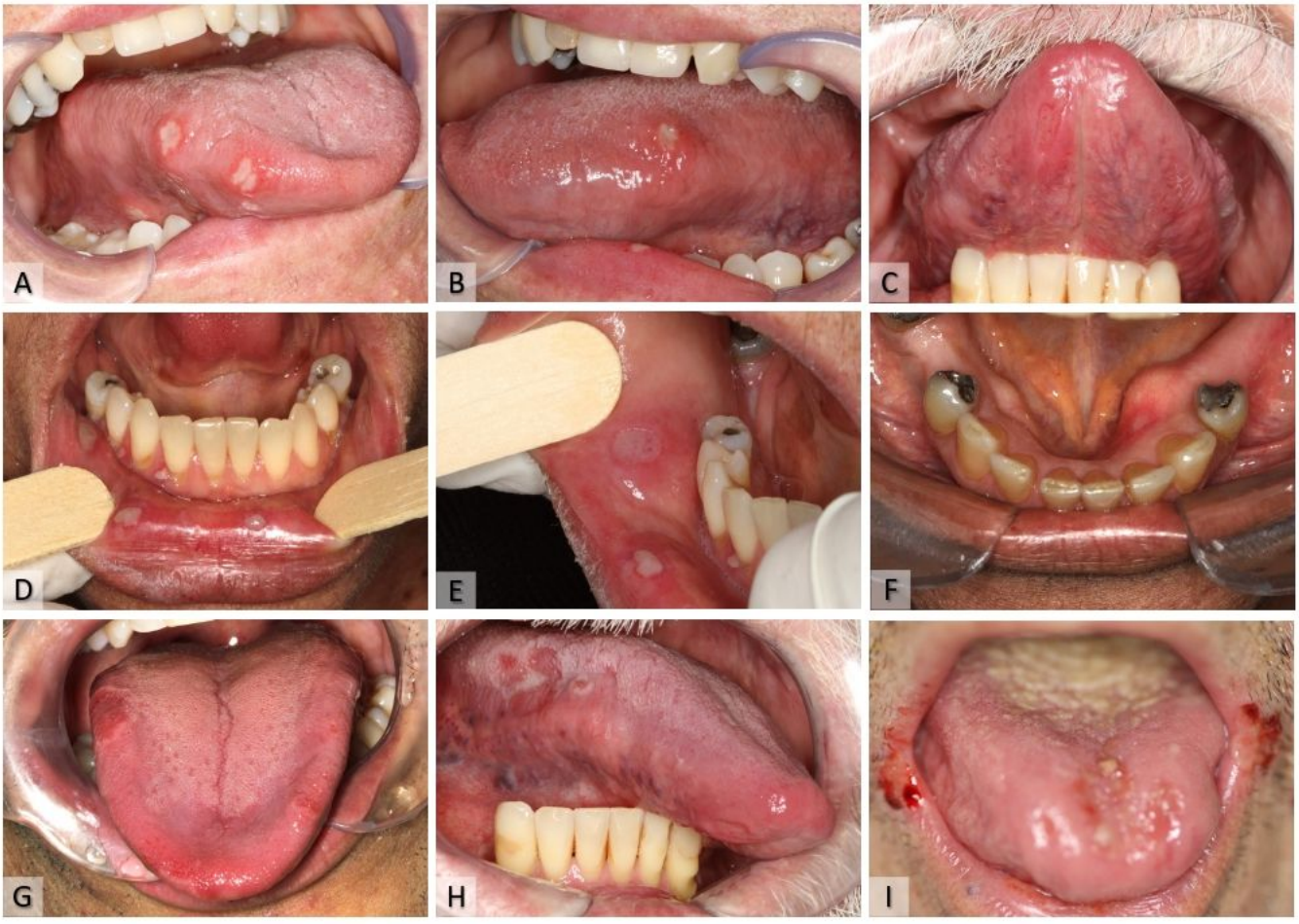

Figure 2

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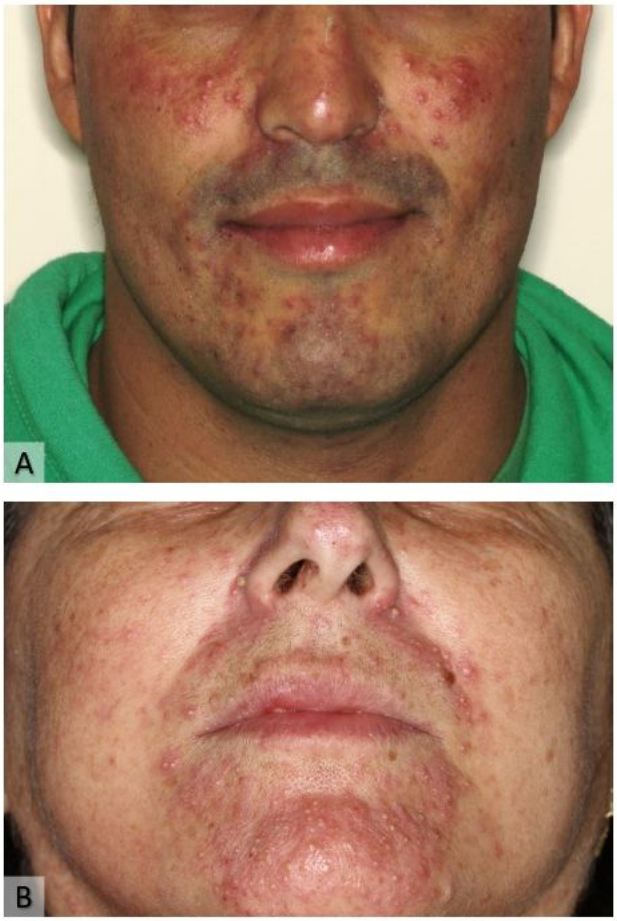

Figure 3

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