Support Care Cancer (2016) 24:4825–4830
DOI 10.1007/s00520-016-3337-5

ORIGINAL ARTICLE

Chronic oral mucositis after radiotherapy to the head and neck: a new insight

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Received: 7 February 2016 / Accepted: 10 July 2016 / Published online: 30 July 2016

Abstract
Purpose Oral mucositis is a major complication of anticancer therapy yet the literature focuses on immediate (acute) mucosal changes and hardly describes the chronic form. We aim to report the clinical manifestations of *chronic mucositis*.
Methods A retrospective chart review of oral mucositis referrals was performed. Inclusion/exclusion criteria defined the patients that were considered to have chronic mucositis.
Results Four female patients treated for tongue/lower lip squamous cell carcinoma were included. Extensive painful oral mucositis lesions developed in all patients during the course of radiotherapy, with ulcers remaining for 5–24 months after completion of therapy. We describe two presentations, namely the *persistent form* (long-lasting ulcers continuing from acute ulcers) and the *recurrent form* (new discrete ulcers appearing on atrophic mucosa following the completion of radiotherapy).
Conclusions The long-term oral complications of radiotherapy to the head and neck may include chronic atrophic, erythematous, and/or ulcerated lesions. A diagnosis of *chronic oral mucositis* should be considered when the lesions are observed at least 3 months after radiotherapy, and other possible etiologies have been excluded. The influence of age and comorbidities (primarily diabetes mellitus) on chronic mucositis, the significance to patient's quality of life, and the management of chronic mucositis are important subjects for future research.

Keywords Chronic · Oral cancer · Oral medicine · Oral mucositis · Oral oncology · Radiation therapy · Radiotherapy

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Introduction

Oral mucositis is a major complication of anticancer therapy and its clinical manifestations include mucosal atrophy, swelling, erythema, and ulceration [1]. Mucositis is associated with pain, may reduce quality of life, and may prevent completion of anticancer therapy [2]. Therefore, extensive research to develop clinical interventions for the management of oral mucositis has been performed [3, 4]. However, this research primarily focuses on the immediate (acute) oral mucosal complications with little, if any, attention paid to the chronic form of oral mucositis. We believe that chronic oral mucositis deserves attention as it may be under-diagnosed and require a different management approach than the acute form. Additionally, its impact on the quality of life of the patient poses a unique challenge for the health care providers. Thus, our aim was to describe the clinical manifestations of this entity and propose a definition of chronic oral mucositis.

Methods

A retrospective chart review of oral mucositis referrals conducted. The inclusion criterion was oral mucositis, with ulcers in the oral mucosae, persisting for more than 3 months after completion of radiotherapy to the head and neck for cancer. Other forms of oral mucositis such as a limited non-ulcerative erythema or atrophy were not included in the study. The exclusion criteria included oral infection (confirmed by laboratory tests), oral manifestation of a systemic infection, chemical trauma, self-inflicted trauma, neutropenia, anemia, nutritional deficiencies (e.g., vitamin B12, folate, iron), ongoing treatment with mammalian target of rapamycin (mTOR) inhibitors or other targeted therapy, or recent (<3 months) cytotoxic chemotherapy and/or radiotherapy.

The demographics, medical background, and clinical presentation as well as the treatment provided and the response to it were retrieved from the patient charts. For the self (subjective) assessment of pain, we used a visual analog scale (VAS), in which "0" represents no pain and "10" represents the most pain imaginable.

All photographic documentation was approved verbally by the patient at the time the photograph was taken. This report was approved by the institutional ethics committee.

Results

Four patients met the criteria and were diagnosed with chronic oral mucositis. The patient characteristics and the clinical features of the mucositis are presented in Table 1 and Figs. 1, 2, 3, and 4. All patients were female and the median age was 74 years (range 44–89). All patients were treated with chemo-radiotherapy (with/without surgery) for squamous cell carcinoma in the oral cavity, three of them in the tongue and one in the lower lip. All patients were non-smokers at time of diagnosis of mucositis (patient #3 has a history of smoking). None of the patients were being given targeted therapy at the time of diagnosis of chronic mucositis.

The pain level reported was either very high (10 out of 10) or none (0 out of 10). The clinical appearance is presented in Figs. 1, 2, 3, and 4 and in Table 1. In patients #1 and #2, the long-lasting ulcers persisted from unresolved immediate (acute) ulcers; we described this type as the *persistent form*. In patients #3 and #4, new discrete ulcers appeared in the oral mucosa after radiotherapy was completed; we used the term *recurrent form* for this type. In the latter form, the atrophic mucosal changes appearing immediately following the radiotherapy remain, whereas the discrete ulcers wax and wane.

Treatment was individualized with systemic pain relief ranging from non-opioid to opioids prescribed. In patient #4, when the oral mucosal ulcers were isolated and painful, topical steroid (0.05 % clobetasol propionate cream, Glaxo-Operations) yielded a good response (i.e., the ulcers healed and the pain was completely relieved). Other oral complications were treated as required (e.g., opioids, local anesthetics, local antiseptics, anti-fungals, dental caries prevention, saliva substitutes).

Discussion

The course of conventional oral mucositis is well known and it differs according to its etiology [5]. Chemotherapy-induced mucositis appears within days and resolves within about 2 weeks, mucositis induced by radiotherapy presents within about 3 weeks and resolves in about 4 weeks after completion of radiotherapy, and targeted-therapy-induced mucositis (stomatitis) involves repeated episodes of ulceration [5]. This may be modified by the following: (a) the specific radiation protocol employed (e.g., normofractionated radiotherapy, altered fractionation, or hyperfractionation protocol), (b) the stomatotoxicity of the agents used and the intensity of the chemotherapy, and possibly (c) patient-related factors (genetics, past-infections, past-treatments) [1, 3, 6]. All signs and symptoms occur immediately following the anticancer treatment and last for days to weeks.

A Spanish study aimed at estimating the incidence of oral mucositis in patients receiving radiotherapy, followed the patients for 2 months after the completion of radiotherapy [7]. The level of pain decreased during the 2 months; however, the patients were not pain free at the end of the period. Likewise, at the 2-month follow-up, the oral mucositis lesions had resolved in 62.3 % of patients, with the remaining third still suffering oral mucositis [7]. The end point in the above mentioned study is actually the starting point for our study, which focused on long-term oral mucositis.

In contrast to the literature about conventional oral mucositis, clinical data regarding chronic oral mucositis are sparse. There have been reports on chronic changes in the post-radiation oral mucosa following the apparent healing of conventional oral mucositis lesions [1]. The oral mucosa becomes friable, i.e., more easily damaged by irritants, and wound healing is compromised [8]. Occasionally, chronic changes, such as atrophy and telangiectasias, may be observed. Patients may experience chronic mucosal neuropathic pain and sensitivity that manifest as a burning or scalding sensation and they may become intolerant to hot, spicy, or acidic food [2]. Yet, oral ulcers have not been reported as typical long-lasting mucosal changes. Pauloski et al. followed 60 patients for 12 months after the completion of radiation therapy and reported very mild persistent mucosal changes, mostly erythema. They noted a correlation between the mucosal changes and functional impairments in eating but not with pain ratings; ulcers were essentially absent from 1 month post-treatment [9]. In another study including 90 radiated patients, van den

Table 1 Patient characteristics and features of mucositis

Feature	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	89	81	44	67
Gender	Female	Female	Female	Female
Cancer type and location	SCC: tongue	SCC: lower lip	SCC: tongue	SCC: tongue
Anticancer modality	RCT; 70 Gy (2 Gy/day for 6.5 weeks); cisplatin	RCT; 70 Gy (2 Gy/day for 7 weeks); cisplatin	Surgery and RCT[a]	RCT[b]; 54 Gy (1.8 Gy/day for 6 weeks); cisplatin
Conventional oral mucositis	Extensive painful ulcers	Extensive painful necrosis and ulcers	Extensive painful ulcers	Extensive painful ulcers
Comorbidities	Aortic stenosis, diabetes mellitus (type 2), glaucoma, hyperlipidemia, pulmonary congestion, renal failure	Diabetes mellitus (type 2), hyperlipidemia, hypertension, ischemic heart disease	None	None
Habits and other local factors in the oral cavity	None; never-smoker	None; never-smoker	Past-smoker	Never-smoker; sharp teeth edges
Chronic oral mucositis (figure)	Fig. 1	Fig. 2	Fig. 3	Fig. 4
Onset	Persistent	Persistent	Persistent (general mucosal changes) and recurrent (ulcer)	Persistent (general mucosal changes) and recurrent (ulcer)
Location	Tongue	Lower lip, floor of the mouth	Tongue, buccal mucosa	Buccal mucosa, gingiva
Manifestations	Extensive shallow ulcer	Extensive necrosis and deep ulcer	Atrophy, erythema, ulcers	Discrete shallow ulcers
Pain (intensity)	Yes (VAS-10)	Yes (VAS-10)	None (VAS-0)	Yes (VAS-10)
Bacterial and fungal culture, HSV PCR	Negative	Negative	Negative	Negative
Management	Tramadol hydrochloride, acetaminophen, NSAIDs	Opioids, acetaminophen, NSAIDs	None (asymptomatic lesions)	Corticosteroid cream
Response to treatment (FU time until response)	Fair (1 week)	Poor (no response were noticed within 4 months)	N/A	Good (2 weeks)
Other post-therapy oral complications	Hyposalivation, oral candidiasis	Limited oral function, lip incompetence	Hyposalivation, restricted tongue mobility	Hyposalivation, rampant dental caries
FU time (after the diagnosis of chronic mucositis)	3 years (deceased)	4 months (deceased)	>1.5 years	>3 years

Fig figure, *FU* follow-up, *Gy* gray, *HSV* herpes simplex virus, *N/A* not applicable, *NSAIDs* non-steroidal anti-inflammatory drugs, *PCR* polymerase chain reaction, *SCC* squamous cell carcinoma, *RCT* radiochemotherapy, *VAS* visual analog scale (0-to-10 scale)

[a] Radiation dose, schedule, and chemotherapeutics were not available

[b] The patient denied surgery

Broek et al. reported "late" mucosal toxicities with slight atrophy in 44 % of the patients, moderate atrophy in 36 %, marked atrophy in 4 %, and ulceration in 4 %; however, the timing post-radiation treatment was not mentioned [10]. These reports are of a shorter duration of chronic oral mucositis than the clinical cases presented here.

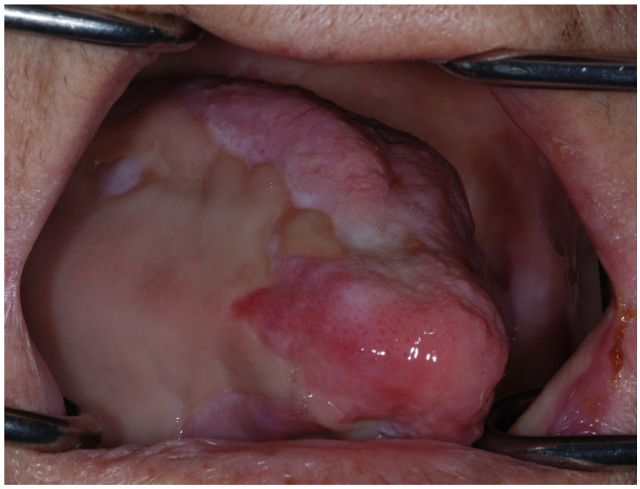

Fig. 1 Clinical appearance of chronic oral mucositis, persistent form, in patient #1, 5 months post-radiotherapy

Based on these cases, we suggest standardizing the time-point from which lesions of oral mucositis are defined as chronic. We propose that the term *chronic oral mucositis* be used to describe an oral mucosal lesion, i.e., atrophy, swelling, erythema, and/or ulceration (as in the immediate acute type of mucositis) which developed or remained at least 3 months post-therapy, after other etiologies have been ruled out.

In agreement with the mucositis pathogenesis model [3], we suggest that the persistent form stems from delayed wound healing, and the lesions of the recurrent form are due to the friability of the post-radiation mucosae [Fig. 5]. Accordingly, the clinical presentation of the persistent form may be similar to the conventional mucositis, whereas the recurrent form shows discrete shallow ulcers that come and go for years following radiotherapy.

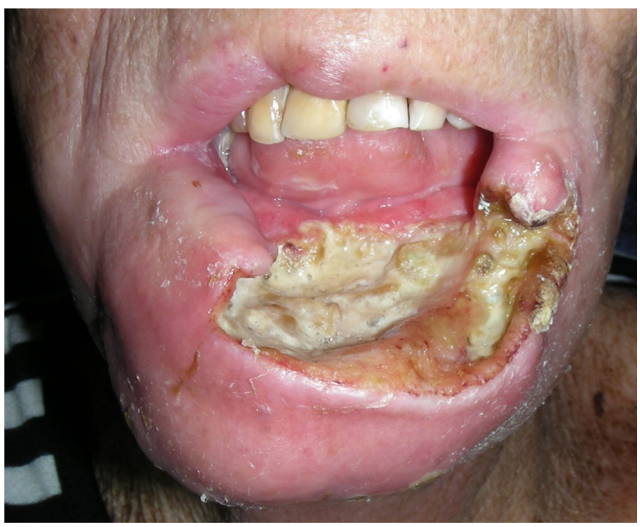

Fig. 2 Clinical appearance of chronic oral mucositis, persistent form, of patient #2 (A), 4 months post-radiotherapy

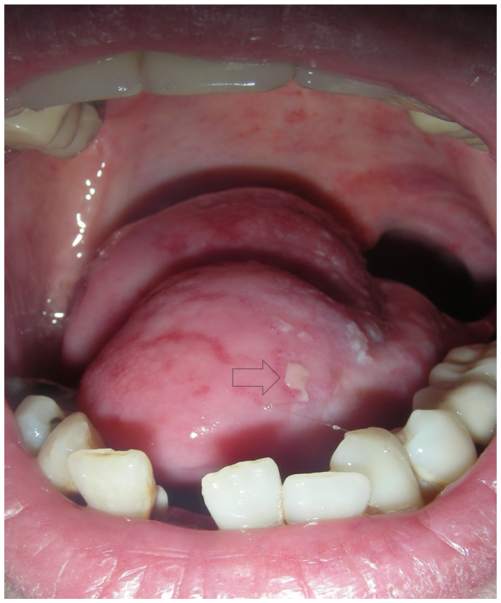

Fig. 3 Clinical photograph of patient #3 at 26 months post-radiotherapy: a discrete shallow ulcer on the tongue mucosa (*arrow*). Note the extensive mucosal changes

Until evidence-based data is available on the treatment of persistent and recurrent forms of chronic oral mucositis, the management approach should refer to the five elements of basic oral care outlined by the Oral Care Study Group of Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) [11]: (1) prevention of secondary infection, (2) pain control, (3) maintain oral function and oral nutritional intake, (4)

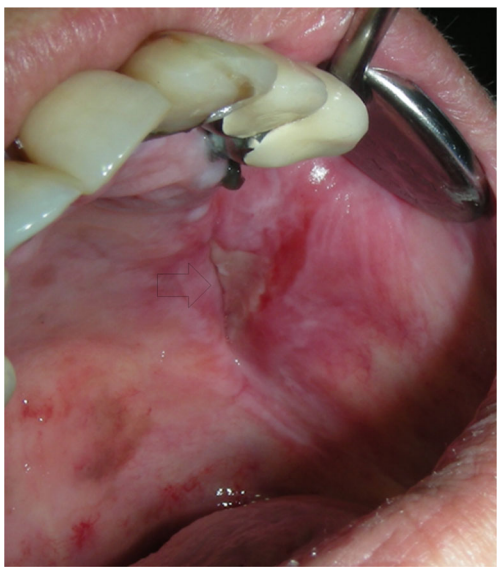

Fig. 4 Clinical photographs of patient #4. Beginning immediate after the radiotherapy, the patient suffered from recurrent discrete shallow ulcers that waxed and waned in various locations of the buccal mucosa. The patient did not use dentures

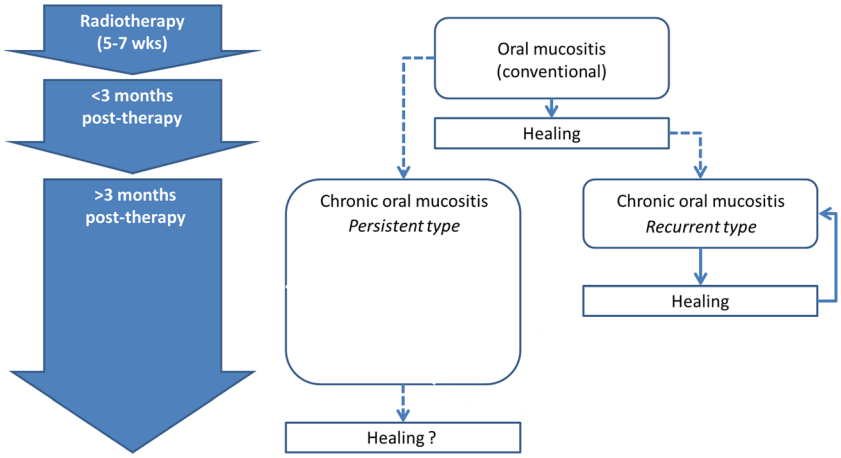

Fig. 5 Timeline of immediate (acute) and chronic oral mucositis. For details, see text. Onset of (conventional) oral mucositis is expected at the second or third week of radiotherapy, manifesting as erythema, epithelial sloughing, and later as ulceration. At about 4 to 6 weeks following the cessation of the radiotherapy, conventional oral mucositis resolves. If ulcers are persist or continuously re-appear after 3 months from radiotherapy, chronic mucositis is suspected

manage concurrent oral complications of the cancer treatment, and (5) improve quality of life. Oral hygiene is of utmost importance in basic oral care. Local traumatic factors and hyposalivation should be addressed as they may contribute to a delayed healing [12]. Topical analgesics/anesthetics (such as 2 % lidocaine mouthwash, 0.2 % morphine mouthwash, 0.5 % doxepin mouthwash) may be helpful [4, 13]. If topical agents cannot relieve pain, systemic medications may be indicated. Considering that chronic mucositis may impair oral function, a nutritionist may be consulted and parenteral feeding may be needed. Treatment strategies that are recommended in radiotherapy-induced oral mucositis may be beneficial in chronic mucositis as well, such as zinc supplement and light therapy [4, 14, 15].

The two patients (#1, #2) with the persistent form of chronic oral mucositis share the following clinical features: gender (female), age (nineth decade), habits (non-smokers), and comorbidity (diabetes mellitus, type 2). Although diabetes mellitus is not considered a risk factor of conventional oral mucositis [16], it is possible that the chronic form of oral mucositis is a manifestation of diabetes-related delayed wound healing or diabetic ulcer. The patients' glycemic control status during the anticancer therapy is not known; however, we can assume uncontrolled diabetes during this period because of improper compliance and the significant alterations to glucose metabolism caused by chemoradiation therapy for head and neck cancer [17]. Accordingly, we suggest using the therapeutic approach for diabetic foot to treat the persistent form of chronic oral mucositis, including intensive glycemic control, hyperbaric oxygen, debridement of necrotic tissue, aggressive treatment of infection, or possibly growth factor administration [18]. However, more research is needed to confirm the association between diabetes mellitus (type 2) and the persistent form of chronic oral mucositis and the efficacy of the suggested therapeutic approach.

Of special interest is the good response observed in patient #4 suffering from the recurrent form of chronic mucositis to a topical steroid preparation. This may indicate that the recurrent form of the chronic mucositis has a different pathophysiology than conventional mucositis, since topical steroids are not effective in the treatment of conventional oral mucositis [19].

The differential diagnosis may include local trauma, infection, drug eruption, neutropenic ulcer, and anemia and/or nutritional deficiencies. Vesiculo-bullous diseases, such as pemphigus or lichen planus, should also be considered. It is important to differentiate chronic oral mucositis from oral neuropathy or irritation due to a dry mouth [20, 21]. Of relevance to the differential diagnosis is the entity named *radiation recall dermatitis*, which is an acute inflammatory reaction affecting only previously irradiated areas. This cutaneous inflammatory condition may be triggered by systemic agents such as cytotoxic chemotherapy or medications [22, 23]. In our patients, there was no late cutaneous involvement and no immediate history of cytotoxics or other medications that were reported in association with recall dermatitis.

A clear definition of chronic oral mucositis will facilitate both communication and treatment. The influence of age and comorbidities (e.g., diabetes mellitus) on chronic oral mucositis, the significance of this complication to a patient's quality of life, and the management of chronic oral mucositis are important subjects for future research.

In conclusion, the long-term oral complications of radiotherapy to the head and neck may include chronic atrophic, erythematous, and/or ulcerated lesions. A diagnosis of *chronic oral mucositis* should be considered when the lesions are observed more than 3 months after radiotherapy.

Compliance with ethical standards All photographic documentation was approved verbally by the patient at the time the photograph was taken. This report was approved by the institutional ethics committee.

Conflict of interest The authors declare that they have no conflict of interests.

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