Bisphosphonate-Mediated Oral Ulcers: A Rare Differential Diagnosis of Erosive Oral Lesions

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Abstract
Oral bisphosphonates are widely used drugs for the treatment of various indications such as postmenopausal osteoporosis. Ulcerations of the upper gastrointestinal tract, predominantly reported for alendronate, are common side effects. The occurrence of ulcerations within the oral cavity is less well known and probably underreported. Especially in cases of incorrect mode of intake, oral bisphosphonates are prone to induce oral ulcerations by as yet incompletely delineated mechanisms. We herein report on 2 elderly female patients suffering from oral ulcerations, which could be attributed to inadequate ingestion of alendronate. Possible ways to cause damage to the oral mucosa include non-specific toxic and pro-apoptotic effects, partly via bisphosphonate-mediated interference with intracellular signalling such as the mevalonate downstream pathway. Adequate patient advice in terms of correct use of oral bisphosphonates is crucial in order to prevent mucosal damage. Otherwise, prompt treatment cessation or a switch to an intravenously administered bisphosphonate is likely to achieve complete healing.

Introduction
Alendronate is a nitrogen-containing amino-bisphosphonate intended for oral administration, which is widely used in female patients with postmenopausal osteoporosis. Other medical indications comprise tumour-related hypercalcaemia and bone metastases [1]. In this respect, bisphosphonates act as inhibitors of osteoclast activity by binding to hydroxypatite [2, 3]. There are three generations of bisphosphonates: first-generation bisphosphonates do not contain nitrogen (e.g. etidronate), whereas second-generation (e.g. pamidronate, alendronate) and third-generation (e.g. zoledronate) bisphosphonates contain nitrogen either within an R1-chain or circularly bound [4].

Common side effects are oesophageal and gastric mucosal irritation [5]. Moreover, bisphosphonate intake represents a major risk factor for the development of bisphosphonate-induced osteonecrosis of the jaw and maxillofacial bone [6]. Cutaneous adverse reactions such as lichenoid eruptions, superficial erythema annulare or erythema multiforme are very rare [7]. Only few case reports, most of which were published in non-dermatological journals, have hitherto been reported on patients with oral ulcerations as side effects of bisphosphonate treatment [8, 9]. Despite the common use of bisphosphonates among several disciplines, oral bisphosphonate-mediated ulcerations may not be well known among dermatologists and, hence, are putatively underdiagnosed, with consequent aggravation of symptoms and prolongation of disease duration.

Oral ulcers are mostly reported after usage of alendronate [9]; however, further bisphosphonates such as etidronate and risedronate [8] have also been mentioned in the literature. Alendronate is supposed to have a higher toxicity to the oral mucosa than risedronate. This is supported by the results of several studies delineating adverse side effects of alendronate with respect to the gastrointestinal mucosa [8, 10].

Here we report on 2 cases of alendronate-mediated oral ulcers in elderly female patients with the aim of bringing the attention of dermatologists to this rare and pre-
sumably sometimes overlooked differential diagnosis when presented with erosive oral lesions.

**Case Reports**

**Patient 1**

Patient 1, a 76-year-old woman, presented with an 18-month history of 2- to 3-cm large, confluent erosions and ulcerations on the lips, gingiva and hard palate covered by a thick haemorrhagic and fibrinous layer (fig. 1). The genito-anal mucosa was not affected. Subjective symptoms were burning, pain, high vulnerability of the oral mucosa and, consequently, significantly impaired eating habits. The patient used to wear a dental prosthesis. Histological examination of a biopsy taken from the edge of the ulcer showed wide mucosal denudation and granulation tissue with overlying fungi on PAS staining; direct and indirect immunofluorescence showed no pathological findings. A preliminary diagnosis of erosive oral candidiasis was made. However, treatment with topical and oral antifungal agents accompanied by thorough oral and prosthesis hygiene measures did not result in any major improvement; subsequent application of topical steroids did not achieve resolution of the lesions either. After 6 months of persistent symptoms additional biopsies were taken from the lower lip, showing reactive acanthosis of the epidermal layer at the edge of an ulcer accompanied by an abundant subepithelial plasmacellular inflammatory infiltrate (fig. 2). Again, direct and indirect immunofluorescence provided no evidence for an autoimmune-mediated skin disease. An infection with herpes simplex virus was ruled out. Bacteriological and mycological swabs showed colonization with *Staphylococcus* species, *Escherichia coli*, *Candida albicans* and *Candida glabrata*, all not being attributed as primarily causative for the clinical findings. In searching for the underlying cause of the oral ulcers, further investigation of the patient’s history was undertaken. Thorough interrogation revealed that the patient’s medication included oral alendronate/cholecalciferol 70 mg once weekly for postmenopausal osteoporosis, which had been started approximately 20 months prior to the development of the ulcerations. During the first month the ulcerations showed short periods of spontaneous healing, but in the course of disease the lesions persisted. Upon further questioning, the patient finally reported letting the tablet dissolve in her mouth before swallowing it. Moreover, she usually wore her dentures during the medication intake. With the clinical suspicion of alendronate-mediated mucosal damage, treatment with alendronate/cholecalciferol was subsequently stopped without replacement. After 4 weeks the ulcerations healed completely and did not recur during further follow-up of 4 years.

![Fig. 1. Lips and gingiva of a 76-year-old patient (patient 1), showing confluent erosions and ulcerations.](image1)

![Fig. 2. Histopathological workup of oral mucosa ulcers of different aetiology.](image2)

**Patient 2**

Patient 2, a 63-year-old woman, presented with a 5-month history of an irregularly shaped, 2-cm large, single, erosive lesion with a yellowish-brown crust covering the hard palate (fig. 3). The genito-anal mucosa and the remaining oral mucosa were not affected. Subjective symptoms were burning, pain, high vulnerability of the oral mucosa and, consequently, significantly impaired eating habits. The patient used to wear a dental prosthesis. Histological examination of a biopsy taken from the edge of the ulcer showed wide mucosal denudation and granulation tissue with overlying fungi on PAS staining; direct and indirect immunofluorescence showed no pathological findings. A preliminary diagnosis of erosive oral candidiasis was made. However, treatment with topical and oral antifungal agents accompanied by thorough oral and prosthesis hygiene measures did not result in any major improvement; subsequent application of topical steroids did not achieve resolution of the lesions either. After 6 months of persistent symptoms additional biopsies were taken from the lower lip, showing reactive acanthosis of the epidermal layer at the edge of an ulcer accompanied by an abundant subepithelial plasmacellular inflammatory infiltrate (fig. 4). Again, direct and indirect immunofluorescence provided no evidence for an autoimmune-mediated skin disease. An infection with herpes simplex virus was ruled out. Bacteriological and mycological swabs showed colonization with *Staphylococcus* species, *Escherichia coli*, *Candida albicans* and *Candida glabrata*, all not being attributed as primarily causative for the clinical findings. In searching for the underlying cause of the oral ulcers, further investigation of the patient’s history was undertaken. Thorough interrogation revealed that the patient’s medication included oral alendronate/cholecalciferol 70 mg once weekly for postmenopausal osteoporosis, which had been started approximately 20 months prior to the development of the ulcerations. During the first month the ulcerations showed short periods of spontaneous healing, but in the course of disease the lesions persisted. Upon further questioning, the patient finally reported letting the tablet dissolve in her mouth before swallowing it. Moreover, she usually wore her dentures during the medication intake. With the clinical suspicion of alendronate-mediated mucosal damage, treatment with alendronate/cholecalciferol was subsequently stopped without replacement. After 4 weeks the ulcerations healed completely and did not recur during further follow-up of 4 years.
Patient 2
Patient 2 was an 86-year-old woman suffering from Alzheimer’s dementia who was hospitalized in a psychiatric unit because of an aggressive behavioural disorder. Her medical history revealed that she suffered from extensive ulcerations of the lips and oral cavity (fig. 3) with consequent painful and impaired swallowing of liquid and food for at least 1 week. Erosions and ulcers were present in a symmetrical distribution at the buccal mucosa, tongue, lips and upper pharyngeal cavity. Wickham’s sign was negative and the genito-anal mucosa was unremarkable. On microbiological examination, there was only bacterial colonization (Staphylococcus species), with no fungal colonization. Indirect immunofluorescence was unremarkable, without any evidence of pemphigus vulgaris or mucous membrane pemphigoid. Further interrogation of the caring nurse revealed an intake of alendronate (70 mg once weekly) for the previous 4 weeks, which had been added to her medication because of mild postmenopausal osteopenia. Due to impaired swallowing, the elderly woman was known to let the alendronate dissolve in her mouth for an unknown period of time before swallowing it or spitting it out. Consequently, upon suspicion of bisphosphonate-mediated oral ulcers, medication with alendronate was stopped promptly. Approximately 4 weeks later nearly all ulcerations had healed and did not recur.

Further Investigations
In addition to conventional haematoxylin and eosin (HE) staining, immunolabelling was performed with an antibody directed against a key molecule of an activated MAPK pathway, i.e. phospho-ERK-1 (Phospho-p44/p42 MAPK – Erk 1/2, Thr202/Tyr204, 20G11 – Rabbit mAb; Cell Signaling, USA) owing to known effects of bisphosphonates on intracellular signalling of the mevalonate and MAPK pathways. In comparison to oral epithelium close to a traumatic ulcer that served as control (fig. 2b), the expression of phospho-ERK-1 was significantly reduced in the lower epithelial layers in patient 1 after topical exposure to alendronate (fig. 2d).

Discussion
Oral application of bisphosphonates has the potential to cause erosions and ulcerations of the oral mucosa. The painful mucosal ulcerations are often irregularly shaped but have well-defined borders and are usually covered by a fibrinous layer surrounded by an erythematous border. Possible differential diagnoses such as infectious, autoimmune and haematono- oncological diseases, as well as mechanical or toxic effects, have to be considered when one is presented with such ulcers. Dental prostheses predispose for fungal infections, but it may be challenging to differ between an erosive oral candidiasis and a secondary colonization of erosions caused by some other disease. Among the autoimmune disorders pemphigus vulgaris is the most relevant one, although the age of our elderly patients is not typical for the primary manifestation thereof. However, pemphigus vulgaris and mucous membrane pemphigoid can be ruled out by means of immunofluorescence and histology.

According to a literature review comprising 13 patients, the time period to the onset of ulcers after starting bisphosphonate therapy ranged from 2 days to 13 months [8]. The most commonly reported locations were the hard palate and the tongue; however, the lips and buccal mucosa – as was the case in our 2 patients – may also be affected [8].

Oral ulcerations are associated with an improper intake mode of bisphosphonates [8]. Correct use implies swallowing the tablets immediately with plenty (minimum one glass, 200 ml) of non-sparkling water in an upright position and staying upright for at least 30 min to prevent reflux with consequent oesophageal irritation leading to ulceration. As some patients have difficulty in swallowing tablets instantly, they instead suck or let them dissolve in the mouth, which results in prolonged contact of the drug with the oral mucosa, promoting irritation, erosion and ulcerations. However, oral ulcerations have also been reported after the assumed correct intake of the drug, hinting at further mechanisms [9]. In the majority of patients, discontinuation of alendronate as well as instruction in the correct intake of alendronate or a switch to an alternative mode of application, i.e. intravenous administration, may lead to clinical remission [8]. After the cessation of bisphosphonate therapy a significant improvement is generally observed within a time period ranging from a few days to a few weeks, whereas time to complete recovery may take up to several months [8, 11]. There seems to be a positive correlation between the time period to complete remission of the ulcer and the duration of the ulcer before the cessation of the drug [8]. The use of dental prostheses, as was the case in the 2 elderly patients presented here, potentially further promotes the development of ulcerations [8, 11].

Bisphosphonates may produce antiproiferative and pro-apoptotic cytotoxic effects on epithelial cells, which are used in tumour therapy. Histological findings in our patients, in accordance with the literature, include ulceration, inflammatory lympho-plasmacellular subepithelial band-like or perivascular infiltrate or chronic granulitis tissue [8, 11]. In vitro studies showed pro-apoptotic effects of bisphos-
phosphonates on murine keratinocytes and gastrointestinal mucosa [12, 13]. Furthermore, it was shown that alendronate leads to a reduction in the proliferation of gingival fibroblasts and oral keratinocytes [13]. Even in clinically healthy oral mucosa of alendronate-treated patients, structural cellular alterations were found [14]. Furthermore, proliferation and regeneration were impaired by bisphosphonates in murine oral keratinocytes [15, 16]. Pabst et al. [13] described an inhibition of viability and migratory properties as well as an increased apoptosis rate of human oral keratinocytes after exposure to nitrogen-containing bisphosphonates like ibandronate, pamidronate and zoledronate compared to non-nitrogen-containing clodronate or control. Interestingly, this correlates with the higher rate of osteonecrosis of the jaw in patients using nitrogen-containing bisphosphonates.

Donetti et al. [14] detected nuclear damage in the upper granular layer without signs of apoptosis, which is in accordance with in vitro data obtained from oral keratinocytes [17]. It is postulated that the toxic side effects on the oral mucosa were partly caused by interference with the mevalonate pathway. Inhibition of the farnesyl-/geranyl-transferase enzyme leads to a decrease in geranylgeranylation, resulting in an impaired association of small GTPases such as Rho and Rac with the cell membrane [13, 18]. An in vitro model of oesophageal epithelium supported the role of the mevalonate pathway in the impairment of cellular properties such as proliferation and survival [19].

In one of our patients (patient 1), immunohistochemical analysis revealed reduced expression of phospho-ERK-1 in the lower layers of the epidermis. The Ras/Raf/MEK/ERK signalling pathway plays an important role in the survival and proliferation of epithelial cells, whereas migration and differentiation are mediated by a Rho-dependent pathway involving RhoA kinase, pERK-1/2 and JNK [20, 21]. Moreover, reduced expression of desmoglein-1 and keratin-10 was observed in human oral mucosa [14]. Desmoglein-1 and keratin-10 are essential for the maintenance of epithelial integrity. Hence, bisphosphate-mediated interference with these pathways may consequently result in complex effects on regenerative, apoptotic and ultrastructural cellular processes, promoting the development and delayed healing of oral ulcers. In summary, the pathogenesis of oral ulcers might be due to either unspecific toxic effects of bisphosphonates or immediate interference thereof with the MAPK and mevalonate pathways, leading to an impaired proliferative capacity of oral keratinocytes and a higher susceptibility to apoptosis.

Conclusion

Before starting oral bisphosphonate therapy it is very important to evaluate which subgroup of patients is suitable for oral therapy. Adequate instruction in the correct medication intake is very important in order to prevent side effects such as oral ulcerations. Especially in mentally impaired patients, the parenteral mode of administration is preferable. Unlike bisphosphate-induced osteonecrosis of the jaw or gastrointestinal damage, oral ulcerations are not widely known and, in particular, are not reported in the dermatological literature. Knowledge of this side effect, which significantly impairs the everyday quality of life, can help to prevent an unnecessary delay in diagnosis and the avoidable administration of ineffective medication.

Statement of Ethics

All clinical investigations were conducted according to the ethical standards of the Declaration of Helsinki.

Disclosure Statement

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References


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