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BISPHOSPHONATE - RELATED MUCOSITIS (BRM): A CASE REPORT

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ABSTRACT

Bisphosphonates (BPs) are the most widely used and effective anti-resorptive agents for the treatment of diseases in which there is an increase in osteoclastic resorption, including post-menopausal osteoporosis, Paget's disease, and tumor-associated osteolysis.

Oral and maxillo-facial surgeons are well aware of the side effects of bisphosphonates and mainly with bisphosphonate-related osteonecrosis of the jaws (BRONJ). Less known are the mucosal lesions associated with the use of these agents. In the scientific literature there are only few reports of mucosal lesions due to the direct contact of the oral form of BPs with the mucosa (bisphosphonate-related mucositis). They are mostly related to improper use of bisphosphonate tablets that are chewed, sucked or allowed to melt in the mouth before swallowing. Lesions are atypical and need to be differentiated from other mucosal erosions.

We present a case of bisphosphonate-related mucositis due to the improper use of alendronate.

Key words: Bisphosphonates, bisphosphonate-related mucositis, mucosal ulceration

INTRODUCTION

Bisphosphonates (BPs) are the most widely used and effective anti-resorptive agents for the treatment of diseases in which there is an increase in osteoclastic resorption, including post-menopausal osteoporosis, Paget's disease, and tumor-associated osteolysis.[1] They significantly reduce the bone turnover and increased the bone mineral density. [1, 2]

These drugs can be grouped in three different classes: first-generation, non-nitrogen containing BPs (e.g., clodronate and etidronate), second-generation nitrogen containing BPs (N-BPs, e.g., pamidronate and alendronate) and third-generation N-BPs (e.g., ibandronate and zoledronate) and the phosphonocarboxylate analogue 3-PEHPC. [1]

First-generation BPs, such as clodronate and etidronate, are metabolized intracellularly to analogues of ATP. The intracellular accumulation of these metabolites within osteoclasts inhibits their function and induces apoptosis, very likely by inhibiting ATP-dependent enzymes. [1] In contrast, second-generation N-BPs, such as pamidronate and alendronate, and third-generation N-BPs, such as risendronate, ibandronate, and zoledronate, interfere with other metabolic reactions, by inhibiting farnesyl diphosphate (FPP) synthase. The inhibition of FPP synthase prevents the prenylation of small GTPases, which are important signaling proteins.[1] The classification of bisphosphonates in this way implies a gradual increase their efficiency. [1]

According to their mode of administration bisphosphonates may be divided into oral and intravenous bisphosphonates [1]. Alendronate, risedronate, ibandronate, etidronate and clodronate are representatives of oral bisphosphonates. Such agents are Fosamax® and Bonviva®. Bonviva® contains ibandronic acid, while Fosamax® contains as active ingredient alendronate. Ibandronate and zolendronate are representatives of intravenous bisphosphonates.

The use of nitrogen containing BPs has been associated with a number of side effects. Oral bisphosphonates, mainly used for the treatment of osteoporosis, have been associated with adverse events involving the upper gastrointestinal (GI) tract, such as nausea, vomiting, epigastric pain, dyspepsia, and esophagitis with esophageal erosions or ulcerations. Other adverse events are hypocalcaemia , secondary hyperparathyroidism, musculoskeletal pain, acute phase response (APR), and ocular events such as nonspecific conjunctivitis, uveitis and scleritis. [1, 3] Oral and maxillo-facial surgeons are well aware of the side effects of bisphosphonates and mainly of bisphosphonate-related osteonecrosis of the jaws (BIONJ). [1, 2, 3]

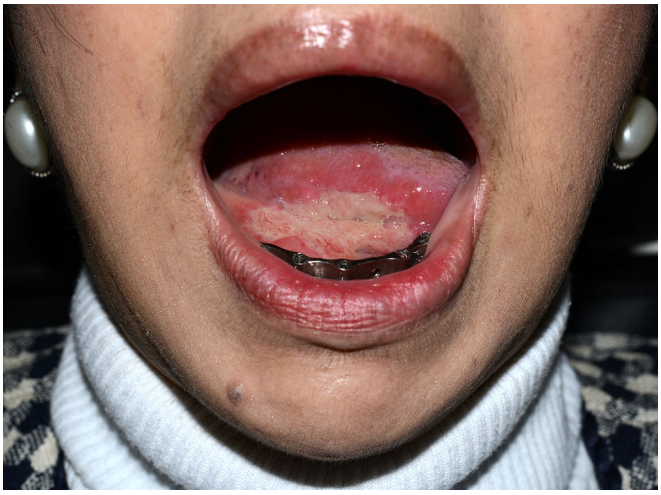
Less known are the mucosal lesions associated with the use of these agents although in the scientific literature there are several reports of such cases. [4, 5]

We present a case of bisphosphonate-related mucositis due to the improper use of alendronate.

CASE REPORT

We present a case of an adult postmenopausal female who is receiving treatment for osteoporosis with Fosamax® (Alendronate). She presented in our office with painful large ulceration on the right lateral border and the ventral surface of the tongue and on the mouth floor that had been present for a few days. (Fig. 1)

Fig. 1. A large ulceration on the right lateral border and the ventral surface of the tongue and on the mouth floor due to the improper use of alendronate



The ulceration was with a flat surface, clear margin, irregular shape, showing slightly white appearance, surrounded by an erythematous halo. The ulcer was unaccompanied by any induration. No irritant factors were apparent in its vicinity.

Other mucosae were not affected. She had no previous history of mouth ulcers, gastric problems and no related skin lesions were present.

After taking a detailed history she complained of difficulty in swallowing the tablet Fosamax® and let it dissolve in the mouth for a while. She reported a thirst and a need of drinking a lot of water afterwards.

The lesion was diagnosed as bisphosphonate-related mucositis caused by the improper use of the drug.

Discontinuation of her medication resulted in rapid healing of the erosions within 2 weeks without any relapse, even on reintroduction and intake of alendronate according to the prescription instructions.

DISCUSSION

The target cells exposed to the effect of BPs are osteoclasts, osteoblasts, osteocytes, vascular endothelial cells, keratinocytes, and macrophages/monocytes. [6]

One of the pathogenesis theories of BRM is based on experimental evidence showing that BPs inhibits capillary angiogenesis, decrease capillary tube formation, and inhibit endothelial growth factors and vessel sprouting. [1] nBP is reported to inhibit the growth of cultured keratinocytes. nBP decreased the number of p63-positive keratinocyte progenitor cells and prevented the gingival fibroblasts from producing keratinocyte growth factor (KGF). [6]

Other studies show that bisphosphonates affect the soft tissues through direct toxicity and direct irritation of oral mucosa, thereby contributing to its erosion and subsequently exposing the bone. [1, 4] Damage to the mucous membranes clinically manifests as mucositis / stomatitis / ulcerations at the site of a prolonged contact. [6, 7]

These lesions are mostly related to the improper use of bisphosphonate tablets that are chewed, sucked or allowed to melt in the mouth before swallowing. [4, 7] Some patients hold them around or under an available denture. [7]

A question arises - whether the usual contact of bisphosphonate tablet with the mucosa could lead to osteonecrosis of the jaw and whether these lesions may be mistakenly diagnosed as osteonecrosis of the jaw (BRONJ). [3]

We found a single publication describing the development of a mucosal lesion after a proper use of oral BPs agent. [5]

In the scientific literature we found a description of an oral ulceration on the lower lip, appeared in a patient with a history of 10 months intravenous infusion of zoledronic acid. [8] This suggests that even the intravenous administration of bisphosphonates may lead to the occurrence of bisphosphonate-related mucositis due to systemic mechanisms of action of these agents. Zoledronic acid caused oral mucosal alteration similar to that caused by the alendronate. [8]

Oral lesions are extremely painful, localized in different places of the oral cavity, at the site contacting with the tablet - palate, tongue, lower lip, oral mucosa and other. [7, 4] The lesions have irregular shape and are covered with pseudomembrane. [9]

The occurrence of the lesions ranges from several days to several months after the beginning of bisphosphonates use. [5]

Lesions are atypical and need to be differentiated from other mucosal erosions-traumatic, infective, aphthous, ulceration related to dermatoses, drug-induced, ulceration as a manifestation of systemic disease, and ulceration due to malignancy.

Traumatic ulceration is caused by mechanical, thermal, or chemical irritants. The most frequent causes are ill-fitting dentures, sharp-edged crowns or bridges, and tooth decay. The ulcer floor is usually clear and ulcer margins do not typically show induration on palpation.[9]

Viral infection is generally associated with multiple small ulcerations. The initial presentation is fluid-filled vesicles, but these rapidly break down to form small, round, painful ulcers with ragged margins that often fuse to form large, irregular ulcers.[9]

Minor aphthous ulceration usually occurs in non-keratinizing epithelium and form small, round or oval ulcers covered with pseudomembrane surrounded by an erythematous halo. They improve within 10—14 days. Similar lesions have been seen in association with various systemic conditions, such as Behcet's disease, Crohn's disease, celiac disease and ulcerative colitis.[9] Major-type aphtha appear as large, painful ulcers and healing may result in mucosal scarring; this type of ulceration can mimic other diseases, such as malignant lesions. [9]

Lichen planus varies in clinical appearance. The typical type of oral lichen planus (OLP) shows bilateral and symmetrical white lace-like patterns of buccal mucosa, but ulceration may be seen in the lesion. This ulceration is usually surrounded by fine reticular white lines radiating from its border. [9]

Some medications and metal allergies can cause similar lesions known as oral lichenoid lesions (OLL).

Pemphigus vulgaris is an autoimmune dermatologic bullous disease. It is characterized by bullae formation that soon afterwards turns into painful, shallow, irregular ulcers with friable adjacent mucosa. Lateral shearing force on the mucosa can produce a surface slough that clinically manifests as persistent erythema (Nikolsky sign). [9]

Many kinds of drugs cause oral ulcerations, including some beta-blockers, immunosuppressants, anticholinergic bronchodilators, platelet aggregation inhibitors, vasodilators, protease inhibitors, antibiotics, NSAIDs, antiretrovirals, and antihypertensives.[9] Oral ulceration can occur as a side effect of treatment with methotrexate. Methotrexate is an antimetabolite and immunomodulating agent, which is increasingly used in the treatment of chronic diseases such as rheumatoid arthritis, psoriasis and others. [9, 10]

Careful examination of the oral mucosa is the most important factor for determining a provisional diagnosis. The number, shape, size, and location of lesions must be carefully observed. The age, sex, and dental and medical histories of the patient may provide useful information.

The effective treatment of bisphosphonate-associated mucositis consists in detecting the improper use of the medication and in encouraging the patient to follow the instructions for dosage and administration, as well as discussing its possible suspension. [5] Lesions heal for several weeks. [4]

As the drug is administered orally, the patient must be instructed well, and be provided with instructions for proper use in order to allow adequate absorption and to reduce adverse effects to a minimum.The tablet should be taken in the morning with at least 200ml of water. The tablet must not be chewed or let dissolve in the mouth. The patient has not to eat or lie down for at least 30 minutes after taking the tablet. The medication intake should be suspended at the least symptom of dysphagia, pyrosis, or retrosternal pain. [4]

CONCLUSION

The oral mucosa is affected by many diseases that may manifest clinically as erosions, ulcerations or mucositis.

The differential diagnosis is broad. Establishing a proper diagnosis requires a detailed history of the patient's complaint, of the progress of the lesions and detailed history of the medications intake and co morbid conditions.

Oral and maxillo-facial surgeons are well aware of the side effects of bisphosphonates and mainly of bisphosphonate-related osteonecrosis of the jaws (BRONJ). Less known are the mucosal lesions associated with the use of these agents. In the scientific literature there are only few reports of mucosal lesions due to the direct contact of the oral form of BPs with the mucosa (bisphosphonate-associated mucositis). The widespread use of oral BPs for the treatment of osteoporosis increases the risk of bisphosphonate-associated mucositis, which motivated us to make this review.

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