Lip Ulceration Associated with Intravenous Administration of Zoledronic Acid: Report of a Case

Dimitrios Andreadis · Stergios Mauroudis ·
Athanasios Pouloupoulos · Anastasios Markopoulos ·
Apostolos Epivatianos

Received: 20 July 2011 / Accepted: 11 November 2011 / Published online: 22 November 2011
© Springer Science+Business Media, LLC 2011

Abstract Although osteonecrosis of the jaw is a well-known adverse reaction of bisphosphonates (BPs), random cases of oral mucosal ulceration after per os administration of BP-aledronate have been attributed to prolonged mucosal irritation. This report, for the first time, describes the mucosal ulceration related to intravenous use of zoledronic acid (ZA). A 52-year-old female patient presented with painful ulcers on both cutaneous/mucosal surfaces of the lower lip and a 2-month history of osteonecrosis of the mandible beside the right lower canine. Her medical record included intravenous administration of ZA for 10 months for primary breast cancer metastatic to bone. Examination of the peripheral blood showed severe anemia and a slightly increased white blood cell count, due to urinary tract infection by *E. coli*, but no evidence of a viral infection. The treatment of anemia and *E. coli* infection did not improve the labial ulcers. Biopsy from the mucosal lesion revealed a non-specific ulceration with moderate inflammatory infiltration. There was no evidence of infection or malignancy. ZA administration was discontinued and within 3 months the lesions were resolved after treatment with systemic antibiotics (amoxicillin), vitamins A and E, clorexidine and H₂O₂ (hydrogen peroxide) solutions and local pantothenic acid/vitamin A creams. Recurrence was detected a month after ZA re-administration. Nevertheless, after new treatment, the patient was free of oral/skin lesions 18 months later. This case, which is the first report of ulceration associated with intravenous administration of bisphosphonates, suggests that systemic mechanisms may be implicated in BP-induced

oral mucosal ulceration. Furthermore, ZA appears to cause the same oral mucosal manifestations as alendronate. This emphasizes the need for oral examination in all cases of BP therapy, whether per os or intravenously administered.

Keywords Bisphosphonates · Zoledronic acid · Oral ulcer

Introduction

Bisphosphonates (BPs) are synthetic analogues of pyrophosphate, with high efficacy in binding bone hydroxyapatite. They inhibit the osteoclastic bone resorption at sites of increased bone remodeling. This negative impact on osteoclast-related bone resorption is mediated by BPs' effect on osteoclast recruitment, differentiation, resorptive activity and apoptosis [1, 2]. BPs are widely used in the treatment of osteoporosis, Paget's disease, multiple myeloma, and bony metastases from breast and prostate cancer or other malignancies [3].

BP-related osteonecrosis of the jaw (ONJ) was described for the first time in 2003 [4]. Although several BPs may cause ONJ, the intravenous administration of nitrogen-containing BPs, including zoledronic acid (ZA) and pamidronate, remain the most common etiologic factors [5]. Mucosal lesions of the upper gastrointestinal tract (esophagus, stomach antrum) presenting as erythema-inflammation, ulceration, and bleeding have been described [6]. Similarly, oral mucosal ulcerations of the tongue, the buccal mucosa, the floor of the mouth, or the lip are thought to be related to orally administered BP (aledronate). These cases have been considered to arise because of incorrect, prolonged, local mucosal exposure or contact with the drug during oral (per os) administration [7–12].

D. Andreadis (✉) · S. Mauroudis · A. Pouloupoulos ·
A. Markopoulos · A. Epivatianos
Department of Oral Medicine/Pathology, School of Dentistry,
Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
e-mail: dandrea@dent.auth.gr; uvomorulin@hotmail.com

The aim of this article is to describe, for the first time, the presence of cutaneous and oral mucosal lip ulcers, accompanying a limited ONJ, in a breast cancer patient undergoing intravenous ZA therapy.

Case Report

A 52-year-old female patient complaining of painful lesions on the lip on both cutaneous and mucosal surfaces was referred to the Department of Oral Medicine/Pathology, School of Dentistry, Aristotle University of Thessaloniki. The lesions persisted over a 2-month period and were not responding to regular treatment using systemic, non-steroidal anti-inflammatory agents, local corticosteroids, antifungal, and antibacterial gels/creams.

The medical record included a mastectomy due to breast cancer 2 years prior, with subsequent bone metastasis, pain, anemia and depression. The patient had interrupted the chemotherapy course 1 year before visiting the clinic and was receiving intravenous ZA at 4 mg-per-month for the last 10 months. In addition, she had been on antidepressants (fluvoxamine, zolpidem, bromazepam) and analgesics (codeine phosphate, acetaminophen, fentanyl) for almost 2 years.

The clinical oral examination revealed two painful ulcers, each 2×1.5 cm in diameter, located on the cutaneous and mucosal surface of the right side of lower lip, respectively (Fig. 1a, b). A similar necrotic lesion of mucosa and bone, smaller in size (1×0.5 cm), was found at the lingual gingiva of the lower, right canine (Fig. 2). No spontaneous healing of these lesions was observed throughout the 2-month period. The patient was wearing partial denture prosthesis placed 3 years before. However, trauma was excluded as a possible etiologic factor, because of the limited use during the last 2 months. Furthermore, ulcers and allergy to dental materials were excluded due to prolonged existence of the prosthesis. The differential diagnosis included fungal, viral or bacterial infection, oral squamous cell carcinoma, and immune-mediated mucocutaneous disease.

Blood examination revealed anemia (Hb 8.6 g/dL, HCT 8.4%, and iron 12 μ g/dL) and slightly increased white blood cell count ($11 \times 10^3/\mu$ l) due to urinary tract infection by *E. coli*. Relevant laboratory tests did not confirm possible viral or fungal infections. The patient underwent treatment with antibacterial agents (doxycycline) for *E. coli* infection, vitamins and iron supplements for anemia successfully increasing Hb/HCT/Fe levels to normal. However, the labial lesions persisted. The histological examination of the partial biopsy taken from the mucosal lesion of the lip showed a non-specific ulceration of the mucosa covered by necrotic pseudomembrane, without

Fig. 1 Ulcers located at cutaneous (a) and mucosal (b) surfaces of the lower lip

Fig. 2 Osseous-gingival necrosis besides the right lower canine

evidence for microorganisms or a neoplastic process. A moderate inflammatory infiltration beneath the ulceration was observed. Reactive and regenerative features were noted in the surrounding tissues (Fig. 3).

The patient was advised to use the partial denture rarely and with the oncologists' permission ZA administration was interrupted. After 3 months of combined use of systemic antibiotics (amoxicillin), vitamins A and E, careful local oral hygiene with oral solutions containing

Fig. 3 Non-specific ulceration of the oral mucosa covered by necrotic pseudomembrane, moderate inflammatory infiltration and regenerative changes in the surrounding tissues

chlorhexidine and H₂O₂ (hydrogen peroxide), as well as application of pantothenic acid/vitamin A creams on the lip, the labial and gingival-osseous lesions were resolved and the patient restarted intravenous administration of ZA. One month later, however, the two ulcerative lesions of the lip recurred and oral candidiasis also developed and was treated by systemic and local administration of antifungal agents for 1 week. The re-application of the above-mentioned local/systemic therapeutic protocol for 8 weeks led to the healing of the lesions. Eighteen months later the patient remained free of oral or skin lesions related.

Discussion

BPs have been successfully used as a treatment option in skeletal disorders including post-menopausal and corticosteroid-induced osteoporosis [13] and Paget's bone disease [14]. Intravenous or oral administration of BPs is commonly used in oncology as a skeletal protector against hypercalcemia and/or bone metastases in cases of multiple myeloma, breast, prostate or other cancers [4].

ONJ is of the most important adverse reactions of BPs, particularly after intravenous ZA (a third generation, nitrogen-containing BP) depending on length of administration and dosage. The management of extended lesions is usually difficult and includes surgical eradication of the necrotic bone, hyperbaric oxygen therapy, and discontinuation of BPs. In contrast, irrigations and prolonged antibiotic therapy are effective in the treatment of limited osteonecrotic areas [7, 15].

Side effects of per os usage of BPs, with regard to soft tissue involvement, include esophagitis, gastric inflammation and bleeding [6]. Also, random cases of oral mucosal

ulceration related to alendronate have been mentioned in the literature. The oral lesions were considered the result of prolonged BP remaining in the oral cavity, due to chewing of the tablet by the patient before swallowing, thus causing local tissue irritation. In our case, oral manifestations including labial ulceration, as well as gingival-osseous necrosis adjacent to the lower right canine are associated, for the first time, with intravenous use of ZA, and not oral alendronate, as in other cases [7–12].

The pathogenic mechanism underlying both osseous and mucosal involvement includes a certain hypothesis. According to this, high concentrations of bisphosphonates in the oral cavity can breach the cohesion of the oral mucosa. A similar mechanism is seen with high bone content of bisphosphonates, which results in similar lesions developed at the overlying soft tissues. Other mechanisms are currently being investigated but are not yet confirmed. Both alendronate and risedronate inhibit cell proliferation in vitro by means of inhibition of farnesyl diphosphonate synthase [16]. ZA has proved to exert a direct cytotoxic effect on epithelial cells and fibroblasts [17, 18] leading to necrosis and apoptosis in vitro [19]. These alterations in the viability of oral keratinocytes and fibroblasts along with the already known anti-angiogenic properties of BPs [20] could inhibit the process of wound healing, increase the risk for secondary infections and necrosis of the exposed bone and/or oral mucosa.

In summary, this case describes the occurrence of cutaneous and mucosal lower lip ulceration and minor ONJ in a patient with metastatic breast carcinoma treated by intravenous ZA. The clinical examination showed that soft tissue lesions did not correlate with osseous necrosis beside the lower right canine. Our case indicates that not only alendronate but also ZA may cause mucosal lesions and ONJ. Moreover, we have shown that oral mucosal involvement was related, interestingly, to the *intravenous* administration of ZA and not to the per os use of BPs, as it is commonly seen after per os alendronate administration. This indicates that not only local irritation but also systemic mechanisms participate in the pathogenicity. Consequently, it underscores the necessity for frequent oral examination, plaque control, and careful oral hygiene during both per os and intravenous BPs' therapy for early diagnosis of ONJ and/or oral mucosal involvement.

References

1. Cremers SC, Pillai G, Papapoulos SE. Pharmacokinetics/pharmacodynamics of bisphosphonates: use for optimisation of intermittent therapy for osteoporosis. *Clin Pharmacokinet*. 2005; 44(6):551–70.
2. Ezra A, Golomb G. Administration routes and delivery systems of bisphosphonates for the treatment of bone resorption. *Adv Drug Deliv Rev*. 2000;42:175–95.

3. Cremers SC, Papapoulos SE. Pharmacology of bisphosphonates. *Bone*. 2011;49(1):42–9.
4. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003;61(9):1115–7.
5. Ruggiero SL, Mebrotra B, Rosenberg TJ, et al. Osteonecrosis of the jaws associated with the use of biphosphonates. A review of 63 cases. *J Oral Maxillofac Surg*. 2004;62:527–34.
6. de Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of aledronate. *N Eng J Med*. 1996;335:1016–21.
7. Kharazmi M, Sjoqvist K, Rizk M, et al. Oral ulcers associated with aledronate: a case report. *Oral Surg Oral Med Oral Pathol Oral Endod*. 2010;110e:11–3.
8. Aleid W, Sidebottom A. Oral mucosal irritation with incorrect use of aledronate. *Br J Oral Maxillofac Surg*. 2009;47:166–71.
9. Garcia-Font M, Curc6 N, Prat C, et al. Mouth sores caused by alendronate. *Actas Dermosifiliogr*. 2009;100:77–83.
10. Treister NS, Richardson P, Schlossman R, et al. Painful tongue ulcerations in patients with bisphosphonate-associated osteonecrosis of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008;105(105):e1–4.
11. Krasagakis K, Kruger-Kragasakis S, Ioannidou D, et al. Chronic erosive and ulcerative oral lesions caused by incorrect administration of alendronate. *J Am Acad Dermatol*. 2004;50(4):651–2.
12. Gonzales-Moles MA, Bagan-Sebastian JV. Aledronate-related oral mucosa ulcerations. *J Oral Pathol Med*. 2000;29:514–8.
13. McClung M. Bisphosphonates. *Arq Bras Endocrinol Metabol*. 2006;50(4):735–44.
14. Silverman SL. Paget's disease: therapeutic options. *J Clin Rheum*. 2008;14(5):299–305.
15. Vescovi P, Nammour S. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) therapy. A critical review. *Minerva Stomatol*. 2010;59(4):181–213.
16. Reid IR, Bolland MJ, Grey AB. Is biphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? *Bone*. 2007;41(3):318–20.
17. Scheper MA, Chaisuparat R, Cullen KJ, et al. A novel soft tissue in vitro model for biphosphonate-associated osteonecrosis. *Fibrogenesis & Tissue Repair*. 2010;3:6–17.
18. Scheper MA, Badros A, Chaisuparat R, et al. Effects of zoledronic acid on oral fibroblasts and epithelial cells. A potential mechanism of biphosphonate-associated osteonecrosis. *Br J Haematol*. 2009;144(5):667–76.
19. Agis H, Blei J, Waltzek G, et al. Is zoledronate toxic to human periodontal fibroblasts? *J Dent Res*. 2010;89(1):40–5.
20. Walter C, Klein MO, Pabst A, Al-Nawas B, Duschner H, Ziebart H. Influence of bisphosphonates on endothelial cells, fibroblasts, and osteogenic cells. *Clin Oral Invest*. 2010;14:35–41.