



# Necrotizing fasciitis as a complication of osteonecrosis of the jaw related to oral bisphosphonate application in a patient with osteoporosis: a case report

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Received: 1 August 2018 / Accepted: 26 September 2018 / Published online: 5 October 2018  
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## Abstract

**Background** Necrotizing fasciitis has been reported as a complication secondary to bisphosphonate-related osteonecrosis of the jaw (BRONJ) in a low number of patients. The only report of such a case in an osteoporosis patient found in current literature was related to short-term bisphosphonate but long time corticosteroid and methotrexate treatment.

**Case presentation** In this article, we report a case of necrotizing fasciitis secondary to osteonecrosis of the jaw related to long-term oral bisphosphonate treatment in an osteoporosis patient additionally suffering from poorly controlled type 2 diabetes. Diabetes mellitus not only has been reported to be a systemic risk factor regarding BRONJ but also to be the most common comorbidity in patients presenting with necrotizing fasciitis and to increase mortality of this condition. Necrotizing fasciitis and BRONJ in the patient could eventually be resolved by a surgical approach and intravenous antibiotic therapy.

**Conclusions** The case presented suggests diabetes mellitus potentially having been an important factor in the particularly unfavorable course of therapy. It emphasizes the importance of an adequate therapy and surveillance of modifiable systemic risk factors like diabetes mellitus in patients being at risk for development of BRONJ. If necrotizing fasciitis is suspected, early diagnosis and aggressive surgical and medical management are essential to minimize morbidity and mortality.

**Keywords** Osteonecrosis of the jaw · Necrotizing fasciitis · Bisphosphonates · Osteoporosis

## Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a rare but severe side effect of bisphosphonate administration, mostly occurring in oncology patients being administered high dose intravenous bisphosphonates (BPs). Osteonecrosis of the jaw related to oral BP treatment has been reported to be less frequent, less severe, more predictable, and more responsive to treatment than intravenous bisphosphonate induced osteonecrosis [1]. Clinical findings in patients with BRONJ, apart from exposed bone, include pain, signs of local

inflammation, intra- or extraoral swelling, the presence of pus, or even abscess formation [2].

Necrotizing fasciitis is a rapidly progressing infection of soft tissue with advancing necrosis of subcutaneous tissue and fascia [3]. It has been reported as a complication secondary to BRONJ in two patients treated with high dose intravenous bisphosphonates for SREs of breast cancer [4, 5], a patient with multiple myeloma [6] and a patient treated with oral BPs for osteoporosis. However, this patient had received BPs for a relatively short period of time and been on a long-term therapy with corticosteroids and methotrexate for rheumatoid arthritis [7].

Diabetes mellitus has been reported frequently as a potential risk factor for BRONJ [8] and in addition has been found to be the most frequent comorbidity in patients with necrotizing fasciitis [9] and to increase mortality in these patients [10].

Up to date, necrotizing fasciitis as a complication secondary to BRONJ has been reported only in patients being treated with high dose intravenous BPs for oncologic diseases and/or

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being administered immunosuppressive medication. In this article, we present the case of a patient with BRONJ related to long-term oral BP-administration for osteoporosis, additionally suffering from poorly controlled type 2 diabetes and showing a particularly unfavorable course of therapy with development of necrotizing fasciitis.

Necrotizing fasciitis can be a severe complication of BRONJ and occur in patients being administered low dose oral BPs and not being administered any immunosuppressive medication as well. Early diagnosis of necrotizing fasciitis may be impeded by the unspecific initial presentation of this potentially life threatening condition that often resembles cellulitis. As the patient's poorly controlled diabetes mellitus presumably has been an important factor for the particularly unfavorable course of disease, hyperglycemia in patients with diabetes mellitus and being at risk for development of BRONJ should raise dentists' and maxillofacial surgeons' particular attention.

In none of the cases reported in current literature, BRONJ has been approached by an extensive surgical therapy regimen. In this article, we present a treatment protocol with extensive surgical treatment of BRONJ, that enabled us to achieve and obtain complete healing of the necrotic bony lesions.

## Case report

A 77-year-old female patient presented to our department with discrete swelling in the area of the right mandible and hypoesthesia of the right mental nerve having occurred 2 weeks before. A previous therapy with oral antibiotics initiated by the patient's general dentist had not led to an improvement of symptoms.

The patient's medical history included antiresorptive treatment for postmenopausal osteoporosis with oral bisphosphonates (alendronate, 70 mg once a week) for 7 years and type 2 diabetes treated with injections of insulin and oral antidiabetics (metformin 850 mg twice a day, glimepiride 1 mg once a day).

According to the patient, a tooth had been extracted in the affected region 7 months prior to the onset of symptoms. Intraoral examination at the time of the patient's first presentation to our department revealed a small intraoral fistula and tenderness on percussion in the right molar region of the mandible.

The panoramic radiograph revealed a slight and cloudy sclerosis in the right mandible region (Fig. 1). A CBCT (cone beam computed tomography) scan, performed to further investigate the bony structures, showed a bone defect following tooth extraction with sclerosis and lingual bone apposition.

Due to the clinical findings, the diagnosis of BRONJ was established according to the AAOMS definition [11] and surgical removal of the necrotic bone was planned.

Aiming at decreasing inflammation prior to the surgical removal of the necrotic bone, an intravenous therapy with penicillin (10 Mio. IU once a day) and metronidazole (500 mg twice a day) was initiated in an inpatient setting. As this regimen markedly decreased the patient's symptoms, the antibiotic therapy was transitioned to an oral application route after 7 days, and the patient left the clinic with the surgical removal of the necrotic bone having been scheduled.

Ten days after her discharge, the patient presented with severe, painful swelling affecting the right submandibular and submental region and in reduced general condition. Laboratory investigations revealed white blood cell count of 19.3 thous./ $\mu\text{l}$  and C-reactive protein 489 mg/l.

Thus, the patient was admitted to our department again and intravenous antibiotic therapy with penicillin (10 Mio. IU once a day) and metronidazole (500 mg twice a day) was initiated. The submandibular space was drained via external incisions under local anesthesia the following day and two drains were placed. Microbiological examination of the swabs taken, besides of anginosus group streptococci, revealed *Prevotella nigrescens* resistant to penicillin but sensitive to metronidazole. Despite changing the intravenous therapy to cefuroxime (1.5 g twice a day) and metronidazole (500 mg twice a day) and antimicrobial purging of the wound twice a day, the patient's symptoms aggravated continuously.

With clinical and microbiological findings being suggestive for necrotizing fasciitis, a second surgical intervention was performed under general anesthesia 2 days after the first surgical drainage. Multiple incisions covering the cervical, supraclavicular, submandibular, and sublingual region were performed and large amounts of putrid and fetid secretion drained. Intraoperative findings, with the underlying fatty tissue and fascia being almost completely necrotic, were consistent with the tentative diagnosis of necrotizing fasciitis. Necrotic tissue was removed completely using curettes and after intensive purging with iodine solution and metronidazole, 4 through-and-through drains were placed (Fig. 2). The patient was transferred to the intensive care unit for postoperative monitoring.

During the course of treatment and with continued intravenous antibiotic therapy and daily antibacterial purges, the patient's condition markedly improved and drains were gradually withdrawn. Antibiotic therapy was terminated 15 days after the patient's admission and the patient was discharged 5 days afterwards.

Eight weeks after the surgical treatment for necrotizing fasciitis the respective region had healed sufficiently to allow for the surgical resection of the necrotic bone. On examination, the patient showed an extraoral fistula in the right submental region, reaching until the mandibular bone

**Fig. 1** Panoramic radiograph showing slight and cloudy sclerosis in the right mandible region



(Fig. 3a) and a punctate mucosa lesion in the molar region of the right mandible (Fig. 3b). A CBCT-scan performed preoperatively revealed a sequestrum caudal to the mental nerve channel and BRONJ like lesions in the right mandible (Fig. 4a).

Surgical treatment was performed under general anesthesia and perioperative antibiotic therapy with penicillin (10 Mio. IU once a day) and metronidazole (500 mg twice a day) was administered starting 2 days before and being continued 5 days after surgery. A periosteoplasty was carried out, with an incision made on the alveolar crest, extending beyond both sides of the area of necrotic bone. Vertical incisions were made to expose necrotic and adjacent bone (Fig. 4b). The affected bone was removed using a bur until healthy, bleeding bone was present, and the edges of the remaining bone were rounded off meticulously (Fig. 4c). Further necrosectomy was performed via an extraoral approach (Fig. 4e, f) and a 13-holes reconstruction plate was inserted for stabilization of the mandible (Fig. 4g). Figure 5 shows the extend of resected bone. Primary intraoral wound closure was performed using the



**Fig. 2** Postoperative conditions 1 day after surgical treatment for necrotizing fasciitis and placement of 4 through-and-through drains

multilayer technique introduced by Voss et al. [12] (Fig. 4d). Postoperative course was uneventful, and the patient was discharged after 5 days.

As the patient was known to have type 2 diabetes, capillary blood glucose monitoring was conducted 3 to 4 times a day during her stay at our hospital. At the day of the patient's second presentation to our department with severe and painful swelling affecting the mandible and with laboratory values showing distinctive signs of inflammation, capillary blood measurements revealed blood glucose levels of up to 492 mg/dl; HbA1c was 8.2%.

During the course of the patient's stay at our hospital, we were able to markedly lower blood sugar levels by controlled administration of the patient's antidiabetic medication. However, capillary blood measurements revealed values exceeding 200 mg/dl at many occasions. At her discharge, the patient therefore was strongly encouraged to consult her endocrinologist for optimization of antidiabetic therapy. When presenting for surgical resection of BRONJ 8 weeks later, HbA1c was 7.3% and again, the patient was encouraged to consult her endocrinologist for further optimization.

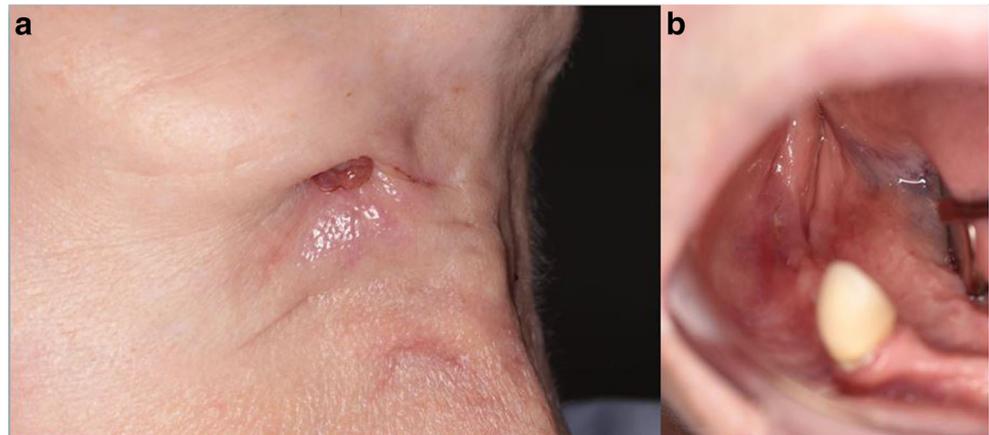
Up on an outpatient follow-up regime, the patient was seen on a regular basis and complete healing of the extra- and intraoral wounds was observed (Fig. 6a–c). No reoccurrence of BRONJ was seen during an 8-month period.

## Discussion

Necrotizing fasciitis as a complication secondary to BRONJ has been reported in a low number of cases. In all these cases, the patients had been administered high dose intravenous BPs and/or immunosuppressive medication [4–7]. Drugs exhibiting immunosuppressive effects, e.g., chemotherapeutic agents and glucocorticoids, have been reported as risk factors regarding BRONJ [13] and might have placed those patients at an increased risk for complications.

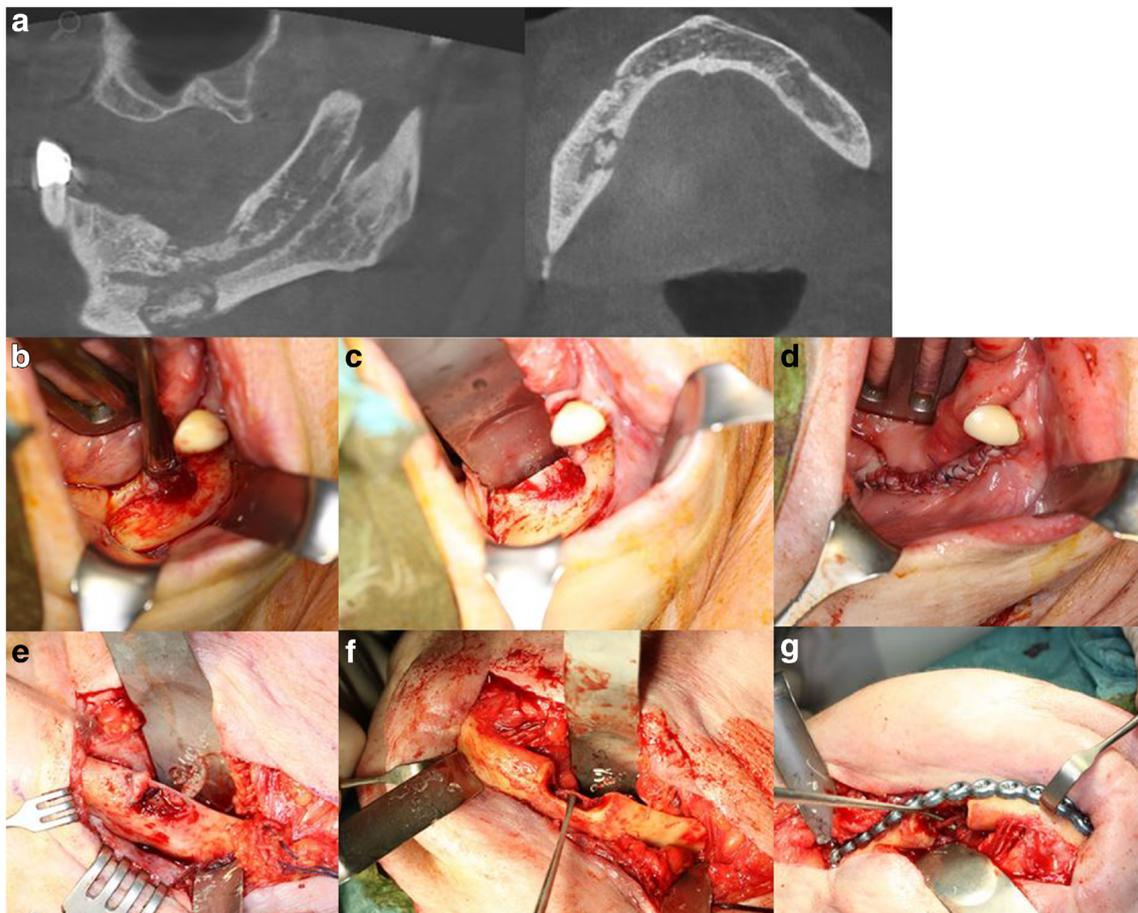
The patient reported in the present article had been on a long-term oral bisphosphonate treatment but not been

**Fig. 3** Extraoral (a) and intraoral (b) conditions 8 weeks after surgery for necrotizing fasciitis showing an extraoral fistula in the right submental region, reaching until the mandibular bone and a punctate mucosa lesion in the molar region of the right mandible



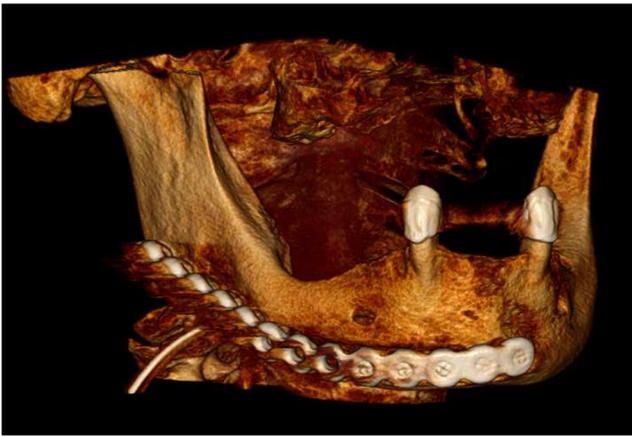
administered any immunosuppressive therapy. However, she presented with poorly controlled type 2 diabetes. Diabetes mellitus, especially when poorly controlled, is known to be associated with immunosuppression, delayed wound healing, impaired microvascular function, and to compromise bone metabolism [8]. It therefore may predispose individuals being administered bisphosphonates to develop BRONJ. Diabetes

mellitus moreover has been found to be the most frequent comorbidity in patients with necrotizing fasciitis [9] and to increase mortality in these patients [10]. The patient's poorly controlled diabetes mellitus thus might have placed her at an increased risk regarding both conditions, BRONJ and necrotizing fasciitis. Diabetes mellitus has been reported in the case presented by Viviano et al. as well, where the patient had



**Fig. 4** Preoperative CBCT scan (a) showing an osteolytic defect and a sequestrum formation in the right mandible. Intraoperative conditions showing removal of necrotic bone via an intraoral approach with

subsequent primary multilayer wound closure (b–d) and an extraoral approach with subsequent insertion of a reconstruction plate (e–g)



**Fig. 5** C-arm CT scan showing the extend of resected bone

developed necrotizing fasciitis secondary to intravenous BP treatment for SREs of breast cancer and eventually died due to multiple organ dysfunction [5].

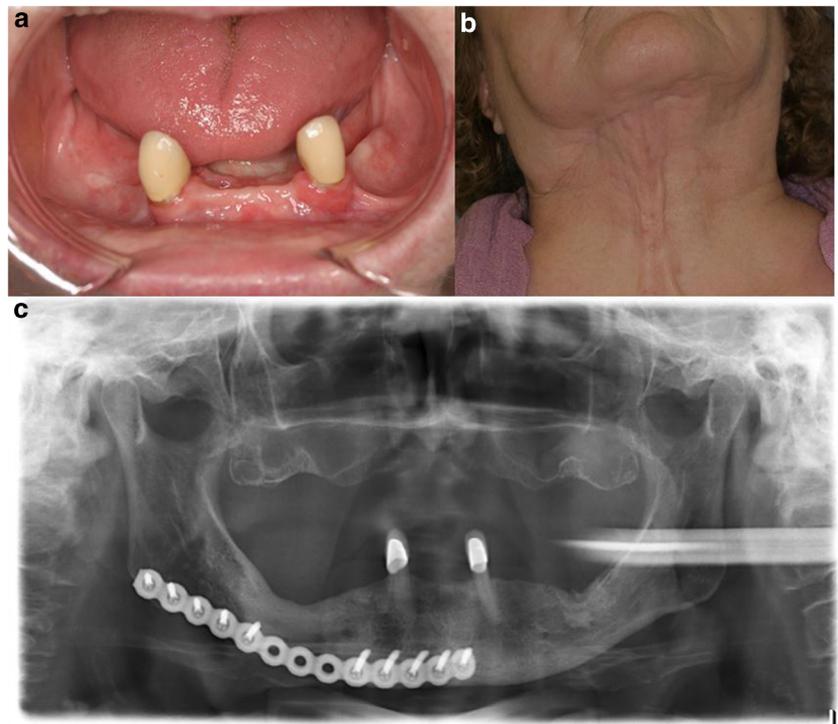
Necrotizing fasciitis of the head and neck is a rare condition mostly originating from odontogenic foci [10]. In the management of this condition, early diagnosis and aggressive surgical and medical treatment are essential, as even with surgery mortality reaches 20–40% and a delayed diagnosis complicates the treatment and increases mortality of this condition [3].

Early recognition of necrotizing fasciitis may be difficult because the initial clinical presentation is not specific and often resembles that of cellulitis [14]. A number of diagnostic tools have been proposed for the recognition of necrotizing fasciitis, including CT, MRI, ultrasonography, and histopathological

examination. However, if clinical signs suggestive for necrotizing fasciitis are present, as it was the case in the patient presented, administration of broad-spectrum antibiotics and surgical exploration should be performed without delay [7].

Odontogenic infections are usually of polymicrobial nature with a combination of aerobic, facultative anaerobic, and obligate anaerobic organisms [15]. This is in accordance with the case presented here, where anginosus group streptococci and *Prevotella nigrescens* were the dominating species. Bacterial colonization is seen as an important factor in the pathogenesis and exacerbation of BRONJ lesion as well, though it is unclear if bacteria induces infection and exposed bone or if exposed bone develops a bacterial biofilm [16]. In the treatment of necrotizing fasciitis, an initial calculated empiric antimicrobial therapy aiming at broad-spectrum antibiotic coverage and often requiring more than one antibiotic should be initiated as soon as possible and modified on the basis of culture and sensitivity tests as soon as these data are available [17]. An antibiotic regimen covering a broad range of bacteria found in odontogenic infections that thus may serve as initial calculated empiric antimicrobial therapy in the treatment of necrotizing fasciitis is the combination of intravenous penicillin and metronidazole. Whereas penicillin G covers streptococci, organisms frequently encountered in infections of odontogenic origin, metronidazole additionally covers the spectrum of anaerobic bacteria [17]. Intravenous administration of a combination of these two antibiotics has been found to have a positive impact on the outcome of surgical BRONJ treatment as well [18].

**Fig. 6** Conditions on follow-up 8 months after surgery. Intra- and extraoral clinical investigation showing complete healing (**a, b**) and panoramic radiograph (**c**) showing a defect consolidation in the right mandible and a reconstruction plate inserted for stabilization of the mandible



A therapy regimen consisting of intravenous antibiotic therapy and extensive surgical debridement/curettage for the treatment of necrotizing fasciitis was successfully applied in the case presented as well as in three of the four cases reported in current literature [4, 6, 7]. However, there is also a report of a lethal course of disease in a oncology patient with necrotizing fasciitis secondary to BRONJ [5].

Information on the definite treatment of BRONJ is only given in two of the cases reported in current literature, with sequestrectomy having been applied in both cases [4, 7]. Regarding BRONJ in general, treatment strategies and aims are still discussed [19, 20]. Whereas conservative treatment with antibacterial mouth rinse, pain medication, and antibiotics is considered a promising option in terms of minimizing symptoms and eliminating infection, it leads to complete mucosal closure only in a low number of patients [21]. In this context, it should be considered that a state of disease with chronically exposed bone may increase the risk of secondary infection [19]. Aiming at complete mucosal closure, many authors prefer surgical treatment of BRONJ lesions, i.e., removal of necrotic bone and primary wound closure [22]. Using this regimen has been found to lead to highest numbers of complete healing of BRONJ lesions (82.1%) [23].

By applying a therapy regimen consisting of perioperative intravenous antibiotic therapy, complete necrosectomy, and primary multilayer wound closure, we were able to achieve and maintain complete mucosal closure in the case presented. Up to date, there is no consensus on the timing of surgical treatment of BRONJ. The routine in our department is not to perform surgery in acute inflamed tissue. This is why we treated the patient's swelling in the area of the mandible and necrotizing fasciitis before approaching BRONJ, intending to perform surgical resection of the necrotic bone after subsidence of inflammation.

This case demonstrates that necrotizing fasciitis as a severe complication of BRONJ may not only occur in patients on high dose intravenous bisphosphonates and/or administered immunosuppressive medications but also in patients with oral BP application and without immunosuppressive therapy. It seems likely that in the case presented, diabetes mellitus has been an important factor for the particularly unfavorable course of therapy. This emphasizes the importance of an adequate therapy and surveillance of modifiable systemic risk factors like diabetes mellitus in patients being at risk for development of BRONJ.

Dentists and maxillofacial surgeons should be aware of the possibility of necrotizing fasciitis as a complication in patients with BRONJ and especially of the fact that the initial clinical presentation of this potentially life threatening condition is not specific and often resembles that of cellulitis. If necrotizing fasciitis is suspected, prompt referral of the affected patient to a hospital providing maximum care is essential, as early diagnosis and aggressive surgical and medical management are crucial to minimize complications.

## Compliance with ethical standards

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

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors. The treatment of the presented patient was not in any way influenced due to this article.

**Informed consent** The patient provided informed consent.

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