

The Role of Inferior Alveolar Nerve Involvement in Bisphosphonate-Related Osteonecrosis of the Jaw

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Purpose: Hypesthesia or anesthesia of the lower lip (Vincent's symptom) is a common sign in patients with osteomyelitis of the mandible, especially in severe cases.

Patients and Methods: We observed an involvement of the inferior alveolar nerve in patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ). Surprisingly, we found Vincent's symptom also in patients with limited and early stages of BRONJ.

Results: These patients were successfully treated by surgical removal of the necrotic bone combined with preoperative and postoperative administration of antibiotics. We report on the occurrence and management of an involvement of the inferior alveolar nerve in patients with BRONJ and discuss possible causes.

Conclusion: We conclude that impairment of inferior alveolar nerve function can be an important early symptom or even the presenting symptom of BRONJ that is also easily detectable by bisphosphonate-prescribing physicians. Concerning the management of BRONJ, we conclude that surgical removal of necrotic bone combined with antibiotics is an adequate treatment in patients with osteonecrosis of the jaw.

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J Oral Maxillofac Surg 67:589-592, 2009

Since the first description of the association between bisphosphonates and osteonecrosis of the jaw by Marx¹ in 2003, bisphosphonate-related osteonecrosis of the jaw (BRONJ) has become a well-known devastating side effect of bisphosphonate therapy and a major clinical problem.^{2,3} The clinical presentation can vary to a great extent, but ulcerations of the gingiva with exposed necrotic bone or intraoral or extraoral sinus tract formation and soft tissue swelling are typical. Some patients have severe pain, whereas some have no pain at all. In addition, abscess formation, pathologic fractures, and impairment of nerve function can occur.^{4,7} How-

ever, impairment of nerve function due to BRONJ has not yet been studied in detail.

Hypesthesia or anesthesia of the lower lip as a sign of certain inflammations of the mandibular bone was first described by Vincent⁸ in 1896. Since then, it has been well recognized in osteomyelitis and other infectious conditions of the mandible.⁹⁻¹¹ In addition, impairment of inferior alveolar nerve function can occur in the course of endodontic treatments and surgical procedures such as third molar removal and orthognathic or trauma surgery of the mandible.^{12,13} However, numbness of the chin can also be an important neurologic sign of cerebral involvement in multiple myeloma or of cerebral metastasis.^{9,14} This is important to keep in mind in patients with BRONJ because most of them receive bisphosphonates intravenously for malignant diseases. The aim of this report is to elucidate the potential role of Vincent's symptom in patients with osteonecrosis of the jaw and to discuss the management of patients who have this condition.

Materials and Methods

Two departments of oral and maxillofacial surgery (Ludwig-Maximilians-University, Munich, Germany, and Horst-Schmidt-Klinikum, Wiesbaden, Germany) took part in this study. Patients with BRONJ and impair-

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0278-2391/09/6703-0019\$36.00/0
doi:10.1016/j.joms.2008.09.028

Table 1. CASE HISTORY OF PATIENTS WITH VINCENT'S SYMPTOM DUE TO BRONJ

Patient No.	Age (yr)	Gender	Disease (Date First Diagnosed)	Bisphosphonate (Dose, Duration, and Application)	Chemotherapy (Duration)	Irradiation (Area)
1	47	F	Breast cancer (June 2006)	Zoledronic acid (4 mg every 4 weeks from March 2006 to June 2006); ibandronate (6 mg every 4 weeks from May 2007 to present)	7 cycles of FAC (May 2006 to December 2006)	Yes (right arm)
2	65	F	Breast cancer (September 2004)	Zoledronic acid (4 mg intravenously every 4 weeks from August 2005 to present)	6 cycles of CMF (December 2004 to September 2005)	No
3	68	M	Multiple myeloma (June 2005)	Zoledronic acid (4 mg intravenously every 4 weeks from February 2005 to present)	No	No
4	50	F	Breast cancer (August 2003)	Zoledronic acid (4 mg every 4 weeks from September 2003 to September 2006); ibandronate (6 mg every 3 weeks from September 2006 to present [paused from August 2007 to October 2007])	4 cycles (epirubicin, docetaxel) (September 2003 to March 2004)	Yes (breast, axilla, and hip)

Abbreviations: FAC, 5-fluorouracil, adriamycin, and cyclophosphamid; CMF, cyclophosphamid, methotrexate, 5-fluorouracil.

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ment of inferior alveolar nerve function (hypesthesia, dysesthesia, or anesthesia) were included. The criteria for the case definition of BRONJ were a history of bisphosphonate intake and exposed necrotic bone in the oral cavity for more than 6 weeks or confirmation of necrotic bone after histologic examination.

The data concerning the medical history and bisphosphonate intake of the patients are given in Table 1. A detailed description of the localization,

complaints (especially concerning impairment of nerve function), therapy, and outcome of the patients is shown in Table 2.

Results

The mean age of our patients with impairment of inferior alveolar nerve function due to BRONJ was 57.5 years. The mean time between the start of intra-

Table 2. LOCALIZATION OF BRONJ, COMPLAINTS, TREATMENT, AND OUTCOME OF PATIENTS

Patient No.	Osteonecrosis of Jaw (Area and Complaints)	Antibiotic Treatment	Surgical Treatment	Outcome
1	Exposed bone region of the mandibular right second molar, almost anesthesia since 5 mo	Amoxicillin/clavulanic acid orally preoperatively and postoperatively	Removal of necrotic bone and extraction of the mandibular right first and second premolars and the maxillary left first and third molars	Complete healing; significant improvement in nerve function
2	Exposed bone region of the mandibular left second molar, hypesthesia and dysesthesia since 5 wk	Sultamicillin intravenously preoperatively, amoxicillin/clavulanic acid orally postoperatively	Local resection of affected area	Complete healing; distinctive improvement in nerve function
3	Region of the mandibular right first molar; pain, swelling, and anesthesia since 2 mo	Sultamicillin intravenously preoperatively, amoxicillin/clavulanic acid orally postoperatively	Removal of necrotic bone and extraction of the mandibular right first and second premolars	Complete healing; noticeable improvement in nerve function
4	Region of the mandibular right second molar; pain, swelling, and hypesthesia since 1 wk	Amoxicillin/clavulanic acid orally preoperatively and postoperatively (intravenously perioperatively)	Extraction of the mandibular right second molar and removal of necrotic bone	Complete healing; complete recovery of nerve function

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venous bisphosphonate treatment and occurrence of Vincent's symptom was 28 months.

Of the 4 patients, 3 had a mild or limited type of BRONJ, with only a small area of affected bone and without severe pain. In these patients Vincent's sign acted as the presenting symptom of BRONJ.

Two patients were immediately referred to a maxillofacial surgeon, and therefore treatment could be started early. In 1 case (patient 1) there was a delay in adequate treatment for 5 months. This was because of the unawareness of the connection between bisphosphonate intake, osteonecrosis of the jaw, and Vincent's sign.

In all 4 patients our treatment regimen, consisting of surgical removal of the necrotic bone combined with preoperative and postoperative antibiotic treatment, resulted in improvement of nerve function as well as the clinical situation. The 2 patients in whom treatment was immediately started showed a rapid improvement of nerve function and recovered quickly and almost completely after surgical removal of the necrotic bone.

Discussion

Since the first description of osteonecrosis of the jaw by Marx,¹ the number of patients with this condition has been rising.³⁻⁵ Vincent's sign is a rare but characteristic and valuable sign of BRONJ because it is detectable by any physician or dentist. Of course, other causes for the impairment of nerve function have to be excluded.⁹ Moreover, our data show that inferior alveolar nerve involvement can occur in early stages and limited types of the disease. This is crucial because early intervention can make a significant difference to the outcome of this entity.¹⁵

The exact pathogenesis of BRONJ is still uncertain.^{3,16} The occurrence of Vincent's sign in early stages of BRONJ and the absence of any impairment of nerve function in severe cases are interesting features but remain unexplained so far. A possible explanation could be the impairment of inflammation and remodeling in and close to the necrotic area due to bisphosphonate effects whereas the inflammatory response can take place close to the nerve channel.

Up to now, not only the theories concerning pathogenesis but also the recommendations for the management of BRONJ have been controversial. Some authors prefer a conservative treatment regimen including local irrigations, long-term antibiotic treatment, and only superficial curettage of necrotic bone parts,⁵ although this treatment regimen has only rarely led to complete healing.^{4,16} In contrast to these statements, we recommend removal of the necrotic bone parts and wound closure accompanied by preoperative and postoperative antibiotic treatment. Preoperative antibiotic treatment is needed because it takes some time to reach therapeutic antibiotic levels

in a pharmacologically deep compartment such as bone, especially in parts with a poor blood supply such as osteonecrotic jaw lesions. Removal of the necrotic and often infected bone is recommended to prevent relapses because necrotic bone is unable to support wound healing and is prone to bacterial infection. Postoperative antibiotic treatment is necessary to protect the bone against reinfection during wound healing and should not be stopped too early because intraorally exposed necrotic bone is often colonized or infected by actinomyces and wound healing in patients receiving bisphosphonates is delayed possibly because of the anti-angiogenetic effects or impairment of bone remodeling.

We conclude that Vincent's sign is an important clinical feature in patients who receive bisphosphonates because it can be an early symptom or even the presenting symptom of bisphosphonate-related osteonecrosis of the mandible. In contrast to the conservative, and often unsuccessful, treatment guidelines, we also conclude that complete surgical removal of the necrotic and often infected bone combined with preoperative and postoperative administration of antibiotics can lead to a distinct improvement and even to complete healing of BRONJ lesions.

Acknowledgment

The authors thank Drs M. Ehrenfeld and W. Winter for proof reading of the manuscript.

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