

Case Report

Gingival squamous cell carcinoma induced by zoledronic acid treatment of breast cancer with brain metastasis: a case report and review of the literature

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Received August 16, 2016; Accepted October 10, 2016; Epub December 1, 2016; Published December 15, 2016

Abstract: Zoledronic acid is prescribed to reduce bone resorption and improve bone remodeling and has recently been used to treat breast cancer. A female patient had bone-metastatic breast cancer complicated by osteonecrosis of the jaw and gingival squamous cell carcinoma (SCC) after receiving zoledronic acid. This 28-year-old patient was diagnosed with *HER2*-positive invasive breast cancer and underwent surgery and radiotherapy. More than 3 years later, she developed brain and skull tumor metastases and received eight cycles of zoledronic acid plus whole-brain radiation therapy and six cycles of combination chemotherapy and zoledronic acid. Eight months later, she had a jaw-related problem and was diagnosed with osteonecrosis of the jaw and gingival SCC in the left jaw. Although the zoledronic acid induced jaw and gingival squamous cell carcinoma, it led to much better overall survival than the average 4-6 months in such patients.

Keywords: Zoledronic acid, gingival SCC, drug side effect, case report, breast cancer

Introduction

Breast cancer is one of the most significant health problems among women [1], and advanced stages of the disease frequently lead to distant metastases, including to the brain [2]. Survival of breast cancer patients depends on cancer type, disease stage, and patient age [2]. Clinically, breast cancer treatment usually consists of surgical resection, chemoradiotherapy, targeting (anti-*HER2*/neu) therapy, and/or hormone blocking therapy depending on disease stage, molecular diagnosis (such as estrogen receptor, *HER2*-positivity, and progesterone receptor statuses), and patient age [3-7]. For estrogen receptor-, *HER2*/neu-, and progesterone receptor-positive breast cancer, current targeting therapies could effectively control disease progression and lead to a favorable prognosis, whereas triple-negative breast cancer usually leads to poor survival [3]. Zoledronic acid was recently used to treat breast cancer patients with bone metastases and it signifi-

cantly improved pain scores and quality of life [8-10]. Indeed, other studies supported the utilization of zoledronic acid for controlling breast cancer; for example, Tonyali et al. showed the effect of zoledronic acid as adjuvant treatment for breast cancer [11], while Delea et al. reported the cost-effectiveness of zoledronic acid plus endocrine therapy in premenopausal women with hormone-responsive early breast cancer [12]. Zoledronic acid was also used to prevent aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole [13]. However, zoledronic acid treatment carries the risk of severe renal impairment [14]. Rare complications have been recently observed in cancer patients treated with bisphosphonates, such as osteonecrosis of the jaw [15, 16] or atypical fractures [17]. Here we describe the case of a woman with breast cancer complicated by osteonecrosis of the jaw and gingival squamous cell carcinoma (SCC) after zoledronic acid treatment.

Zoledronic acid-induced gingival SCC

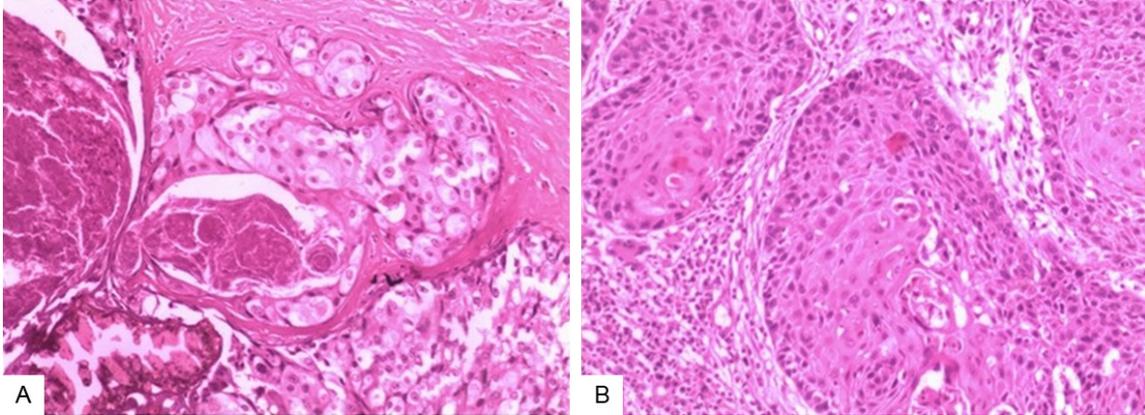


Figure 1. A. Histological examination showed breast ductal carcinoma in situ with invasive component. (H&E, $\times 100$). B. Histological examination showed squamous cell carcinoma. (H&E, $\times 100$).

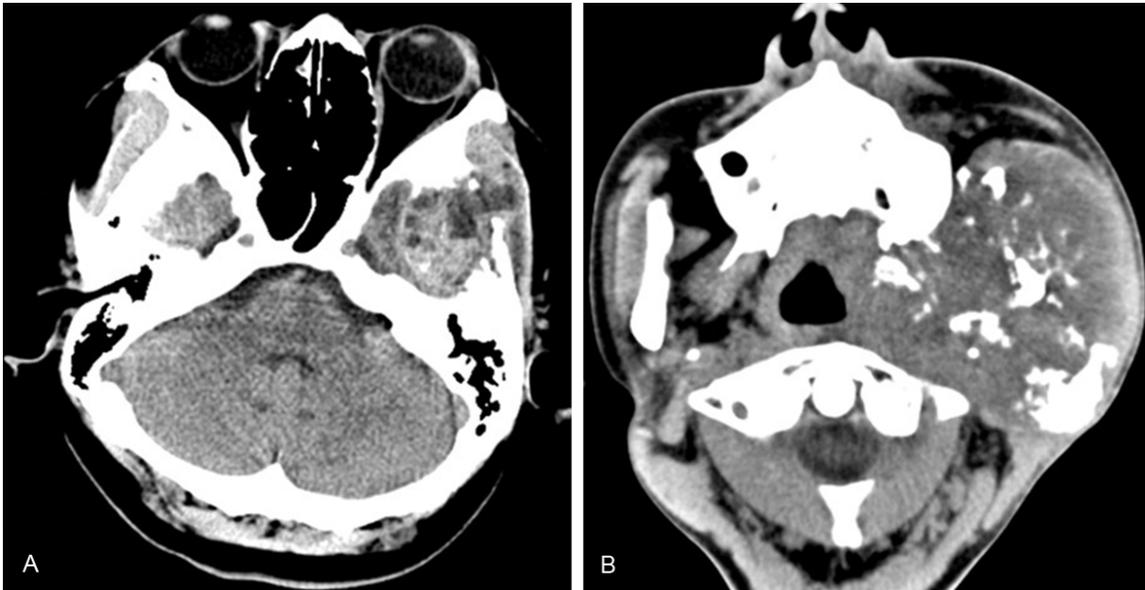


Figure 2. A. A computed tomography (CT) scan was used to diagnose breast cancer-related brain and skull metastases. B. A CT scan was used to diagnose gingival squamous cell carcinoma.

Case report

In August 2010, a 28-year-old woman felt a mildly painful soybean-sized nodule in the bottom of right quarter of the mammary gland during a self-examination. Four months later, the nodule became larger and she sought medical attention. In the hospital, she was diagnosed with breast cancer and underwent a modified radical mastectomy of the right breast. The pathology report of the surgical tissues confirmed the diagnosis of breast ductal carcinoma in situ with invasive component but without any axillary lymph node involvement or tumor

metastases (0/4) (**Figure 1A**). Immunohistochemical staining of tissue specimens showed that the breast cancer was ER (-), PR (-), C-erbB-2 (+++), and p53 (++). Thereafter, the patient underwent postoperative radiotherapy of the right breast and lymphatic drainage area for a 200 cGy dose for a total dose of 50 Gy. At a March 2014 follow-up appointment, she reported a headache and left-sided tinnitus. A computed tomography (CT) scan showed a shadow with intermediate density in the left temporal lobe surrounded by edematous tissue and bone destruction in the left temporal bone (**Figure 2A**); thus, she was diagnosed with

breast cancer metastasizing to the brain and skull and then further treated with paclitaxel 240 mg and pirarubicin 70 mg plus 4 mg (two cycles) and zoledronic acid 4 mg once a month. On April 14, 2014, she also underwent whole-brain radiotherapy with a total dose of 30 Gy. Thereafter, she was continuously treated with paclitaxel 240 mg and pirarubicin 70 mg for four cycles plus zoledronic acid 4 mg once a month. In January 2015, she had difficulty opening her mouth (only one finger could be inserted) and reported slight swelling of the left cheek and pain in the left mandibular region. Thus, osteonecrosis of the jaw was suspected and the zoledronic acid treatment was stopped. However, she had progressive symptoms of left cheek swelling and stiffness. A physical examination showed a left alveolar bone mass with pain and sore gums. A CT scan revealed cranial bone destruction and 5.5 × 6 cm lesion in the left nasopharynx under the left zygomatic arch and parapharyngeal space (**Figure 2B**). In March 2015, she was further treated with two cycles of 120 mg duoxitasai and 90 mg cisplatin. However, the patient responded poorly to the treatment and a CT scan showed left facial bone destruction with a tumor. The pathology report of the tissue biopsy confirmed the diagnosis of SCC (**Figure 1B**) independent of breast adenocarcinoma. The patient was further treated with radiation therapy of 200 cGY for a total dose of 60 GY plus 50 mg cisplatin for four cycles.

Discussion

Here we showed a rare case of a breast cancer patient with zoledronic acid-induced SCC of the jaw. Due to advancement in surgery, radiotherapy, chemotherapy, and endocrine and other systemic treatment in recent decades, the overall survival rate of patients with metastatic breast cancer is continuously improved; however, breast cancer with brain metastases remains a serious and devastating complication that affects quality of life and increases mortality rates [2]. The 1- and 2-year survival rates of such patients are 20% and 2%, respectively [18]. A large number of studies previously confirmed that *HER2/neu* overexpression in breast cancer tissues contributed to poor survival, frequent tumor relapse, a high brain metastasis rate [19], and poor prognosis. After receiving a diagnosis of *HER2/neu*-positive

breast cancer metastasizing to the brain, patients often receive palliative treatment. However, to date, due to the application of molecular targeting drugs. Patients with *HER2/neu*-positive breast cancer show better overall survival rates than those with *HER2/neu*-negative patients [18, 20], especially the addition of radiotherapy that can increase the degree of drug permeability across the blood-brain barrier [21]. A previous study also showed that breast cancer patients with brain metastases had a higher overall survival rate than those with brain metastases from other tumors [22]. The patient in the current study had *HER2/neu*-positive breast cancer but did not receive Herceptin treatment due to financial issues; additionally, her brain metastases were well controlled even 18 months after the standard radiation and chemotherapy regimen and no signs of recurrence were seen. This finding indicates that treatment after brain metastasis is necessary and sufficient to improve the survival of breast cancer patients with brain metastases.

Furthermore, bisphosphonate drugs can inhibit osteoclast function and retard the bone resorption and remodeling processes but increase bone mineral density; thus, they are widely utilized to treat diseases related to abnormal bone metabolism such as myeloma, cancer hypercalcemia, malignant tumor osteolysis, tumor-to-bone metastasis, osteoporosis, and Paget's disease [23]. With the wide applications of these drugs, some adverse reactions gradually begin to appear. Since the first report of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in 2003 [15], increasing effects have been reported, including severe renal impairment [13] or atypical fractures [17] caused by the zoledronic acid treatment. BRONJ is identified when a patient with a history of bisphosphonate drug treatment for >8 weeks shows bone necrosis in the oral cavity but has no history of radiation therapy in the head and neck region [15, 24]. The patient in our current study met this definition: She took zoledronic acid eight times and then experienced left mandible swelling and related issues. After a tissue biopsy, she was diagnosed with SCC of the jaw. However, it is worth further investigating whether the SCC of the jaw in the left posterior gums was related to the BRONJ or the zoledronic acid treatment.

The mechanism of zoledronic acid treatment-associated BRONJ may be related to its potential anti-angiogenic properties [11]. Basso et al. [25] demonstrated that the serum levels of vascular endothelial growth factor and basic fibroblast growth factor significantly decreased in patients after receiving zoledronic acid. This property of zoledronic acid could be also the basis for its anti-tumor activity. The decrease in tissue angiogenesis could lead to a reduction in oxygenated blood in this part of the body. On the one hand, it leads to a weak acid condition in the tissue, the main factor for tumor cell growth. A recent study suggests that a low pH value can induce a cancer stem cell phenotype and make it easier to maintain tumor cell heterogeneity [26]. On the other hand, a lack of oxygen in the cells can activate hypoxia inducible factor (HIF)-1 expression, which regulates blood vessel formation [27]. HIF-1 can also participate in epithelial-mesenchymal transitions (EMT) by regulating a variety of signaling pathways [28] and gene transcription activities. Changes in tissue oxygen levels in the microenvironment could signal the HIF-1-induced hypoxia signaling pathway to induce and regulate cellular EMT. A previous study showed that EMT played a key role in the tumor development, progression, and metastasis [28]. Thus, zoledronic acid may induce tumorigenesis. In conclusion, this study shows a rare case of female patient with breast cancer that metastasized to the brain in whom SCC of the jaw occurred after zoledronic acid treatment. However, further studies are needed to confirm whether zoledronic acid can induce tumorigenesis in humans.

Acknowledgements

This work was supported by grants from Science and Technology project of Liaoning Province (No. 2015010336) and Education Science planning project of Liaoning Province (No. JG14DB254).

Disclosure of conflict of interest

None.

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