Osteonecrosis of the jaw associated with everolimus: A case report

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Abstract. Everolimus, a mammalian target of rapamycin inhibitor, has recently been approved for the treatment of metastatic estrogen receptor-positive breast cancer, at a daily dose of 10 mg in combination with exemestane. Osteonecrosis of the jaw (ONJ) is a rare but severe condition, characterized by exposed necrotic bone, and is associated with various drugs that are often used to treat advanced malignancies. We herein report the case of a patient with breast cancer who developed ONJ during treatment with everolimus, which improved after discontinuation of the drug. To the best of our knowledge, this is the first reported case of everolimus-associated ONJ in a patient receiving everolimus for metastatic breast cancer. In 2014, an 80-year-old woman was started on treatment with everolimus and exemestane for stage IIB estrogen receptor-positive breast cancer. Within 2 months, the left side of her face became edematous, with localized heat and tenderness of the left mandibular region and a 3-mm round area of exposed bone. There was purulent discharge and the surrounding gingiva was edematous and erythematous. The left mandible exhibited a low signal intensity area on T1-weighted magnetic resonance imaging. Treatment was discontinued and ONJ showed improvement after 2 months. Therefore, when prescribing everolimus for metastatic breast cancer, oncologists should be aware of the possibility of ONJ as a complication.

Introduction

Breast cancer (BC) is the most common cancer affecting women worldwide and is the second leading cause of cancer-related mortality in women (1-3). Approximately 30% of all patients with BC develop metastasis, with a mean survival time from the diagnosis of recurrence of 18-30 months (1-4). Therefore, treatment provided to patients with metastatic BC (MBC) aims to prolong survival, while relieving symptoms and maintaining a good quality of life.

Aberrations of the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway are common in BC, and increased PI3K/AKT/mTOR signaling is associated with resistance to hormone therapy and human epidermal growth factor receptor 2 (HER2)-targeted therapy (5). Based on results of the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study (5), the mTOR inhibitor everolimus (combined with exemestane) has been approved for the treatment of advanced hormone receptor-positive/HER2-negative BC that has shown progression with prior non-steroidal aromatase inhibitor therapy. Osteonecrosis of the jaw (ONJ) is a serious condition characterized by exposure of necrotic bone. Although ONJ is rare, it is associated with various drugs that are often used to treat patients with advanced malignancies (6,7). ONJ associated with antiresorptive agents is most often found in patients who are on bisphosphonate therapy. However, ONJ caused by molecular-targeted (anti-angiogenic) agents, such as sunitinib (a multikinase inhibitor) and bevacizumab [a monoclonal antibody targeting vascular endothelial growth factor (VEGF)], has recently been reported in patients who have never received bisphosphonates (8-10). We herein report the first case of ONJ in a patient receiving treatment with everolimus for MBC.

Case presentation

In 2001, a 67-year-old woman underwent mastectomy and axillary lymph node dissection for stage IIB estrogen receptor-positive cancer of the right breast. In March, 2011, the patient developed metastases to the lymph nodes and chest wall. She consecutively received capecitabine and two lines of hormone therapy, including tamoxifen and fulvestrant. In December, 2014, administration of everolimus (10 mg/day) plus exemestane (25 mg/day) was initiated. After 2 months, the left side of her face became edematous, with localized heat and tenderness in the left mandibular region, as well as a round 3-mm area of exposed bone. There was also purulent discharge, and the surrounding gingiva was edematous and erythematous. On T1-weighted magnetic resonance imaging, a low signal intensity area was identified in the left mandible. The patient had no relevant past dental history, such as tooth extraction. To rule out metastasis, an incisional biopsy specimen was obtained by an otolaryngologist. The pathological

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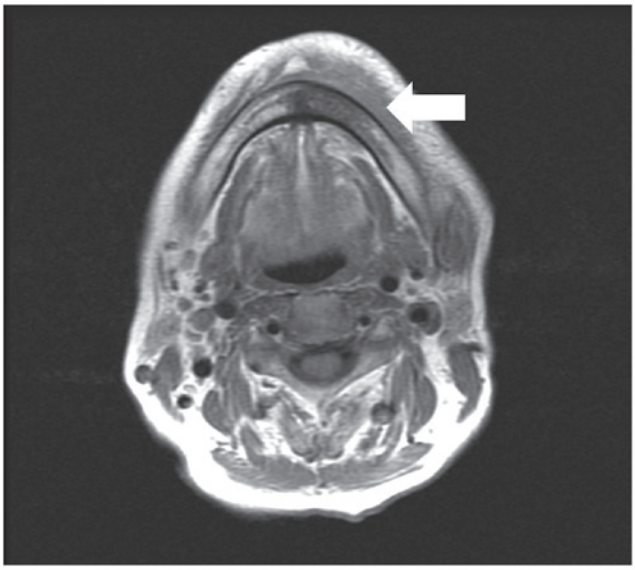

Figure 1. T1-weighted image showing a hypointense area in the left mandible (white arrow), corresponding to focal osteonecrosis.

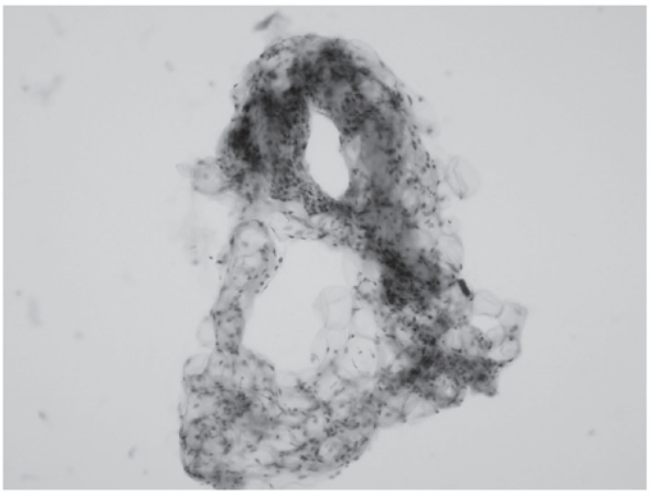

Figure 2. Microscopic examination revealed chronic non-specific inflammation. There was no evidence of malignancy.

examination revealed chronic non-specific inflammatory cells with no evidence of metastasis; thus, ONJ was diagnosed. Treatment with everolimus and exemestane was discontinued and cephalosporin was administered for 2 weeks. The acute inflammation gradually resolved and the exposed bone showed improvement after 2 months.

Discussion

The first case of ONJ was described in 2003 (11). Bisphosphonates and other antiresorptive medications are associated with a risk of ONJ, which is a complex condition involving multiple tissue and cellular responses to wound healing and/or infection. Patients with ONJ develop inflammation with exposure of the bone affecting the mandible, maxilla, or both, in the absence of previous radiation therapy or metastasis. Cancer patients have been reported to be at a higher risk for ONJ, with a prevalence of 1.5%. In Australia, an average prevalence of 1.15% was reported in cancer patients, reaching 7.8% in those undergoing dental work (11,12). In another study, patients with myeloma had a prevalence nearly double (55.9%) that of patients with BC (33.4%) or prostate cancer (4.6%), despite all three groups being treated for metastatic bone lesions with zoledronate or pamidronate by the same protocol (12).

ONJ may be easy to overlook at its onset (stage 0), since it presents with chronic inflammation of the gums and slow healing following tooth extraction or implant surgery; paresthesia, odontalgia, or lingual dysesthesia; loss of teeth that cannot be attributed to chronic periodontal disease; or periapical/periodontal fistula not associated with caries. Later stages (1-3) are characterized by necrosis of the jawbone, with yellowish-white areas, suppuration, fistulae in the oral cavity or externally to the skin, and bleeding. Our patient had stage 2 ONJ.

There have been recent reports on the possible association of ONJ with everolimus (13,14). However, bisphosphonates were also administered to the patients in these reports, so the authors were unable to reach a definitive conclusion regarding the cause of osteonecrosis. Therefore, to the best of our knowledge, this is the first reported case of ONJ caused by everolimus. Everolimus inhibits the activity of mTOR, a serine/threonine kinase involved in cell growth and metabolism, resulting in a decrease of VEGF levels and inhibition of the growth and proliferation of tumor cells, endothelial cells, fibroblasts and blood vessels. Everolimus has been approved for the treatment of advanced BC, neuroendocrine tumors of pancreatic origin and advanced renal cell carcinoma.

Preclinical studies in mouse models have demonstrated that inhibition of mTOR reduces the maturation and increases the apoptosis of osteoclasts (15,16), which may be the mechanism underlying the occurrence of osteonecrosis associated with mTOR inhibitors.

There have also been reports of ONJ caused by sunitinib and bevacizumab. On histological examination, the vasculature is intact in ONJ lesions, despite the anti-angiogenic effect of drugs such as bisphosphonates, bevacizumab, sunitinib and everolimus (8,10,17). Therefore, vascular impairment may not play a major role in the development of ONJ (18,19) and further studies are required to elucidate the mechanism of ONJ in patients treated with everolimus.

In conclusion, attention to the possibility of ONJ is required when everolimus is used to treat patients with MBC.

Written consent was obtained from the patient for publication of this report and the related photos.

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