Osteonecrosis of the jaw after radiation followed by bevacizumab

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Abstract

Osteonecrosis of the jaw is a recognized complication associated with bevacizumab. Here, we present a patient with squamous cell carcinoma of the tonsil who experienced minimal skin fibrosis following intensity-modulated radiation therapy. Subsequently, the patient developed rectal adenocarcinoma and encountered osteonecrosis of the jaw after receiving two cycles of bevacizumab. Close monitoring, accompanied by thorough examination to detect early signs of osteonecrosis of the jaw, should be considered for patients who have undergone radiation therapy in the head and neck region and are receiving bevacizumab or other medications known to be associated with osteonecrosis of the jaw.

Keywords: bevacizumab, jaw, medication-related, osteonecrosis, osteoradionecrosis, radiation

Introduction

Osteonecrosis, also known as avascular necrosis, of the jaw is a known complication associated with the use of bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor [1]. Vascular endothelial growth factor plays a vital role in osteogenic differentiation. The anti-angiogenic property of bevacizumab could negatively affect the microvessel integrity in the jaw, compromising osteocyte differentiation and wound healing [1]. Cases of osteonecrosis of the jaw after bevacizumab have been reported in the literature since 2008. Herein, we discuss a patient with osteonecrosis of the jaw, developing after two cycles of bevacizumab therapy four years post radiation therapy.

Case Synopsis

A man in his 60's with a prior medical history of a gastric ulcer and vitamin B12 deficiency, 60-pack year smoking history, previous alcohol abuse, and marijuana abuse was diagnosed with well-differentiated squamous cell carcinoma to the right tonsil with 3cm right jugulodigastric node (4AT1N2A).

The patient underwent a complete dental extraction during the dental evaluation prior to the treatment of head and neck cancer and became edentulous with intact mucous membrane in the oropharynx. He received concurrent chemotherapy with cisplatin and 70Gy of intensity modulated radiation therapy to the right mandible. Subsequently, he experienced significant peripheral neuropathy from the platinum therapy including numbness, tingling, and pain in his throat and jaw. A percutaneous endoscopic gastrostomy tube was placed for nutrition management and later removed when he could tolerate a soft diet. Post radiation, he developed hyperpigmentation with minimal fibrosis of his skin on the right neck and jaw and mild submental edema with no visible mucosal damage.

Three years later, he was diagnosed with a near obstructing moderately differentiated rectal adenocarcinoma (T3N1M1). He began concurrent chemoradiation with capecitabine and oxaliplatin and completed 50.4Gy 3D conformal therapy to his rectum.

Owing to the persistence of the rectal mass and discovery of metastatic colorectal cancer to the liver and lung, he was started on bevacizumab, fluorouracil, and irinotecan with folinic acid. He had intact mucosa in the oropharynx prior to the treatment. After two cycles of chemotherapy with bevacizumab, he developed oropharyngeal pain and purulent discharge along with the small hole in his right jaw. Laryngoscopy revealed no other lesion or mass in the oral cavity. He subsequently experienced tissue exposure in the retromolar trigone and the ascending ramus of the right mandible and ultimately developed osteonecrosis of the jaw (ONJ), [**Figure 1**].

His chemotherapy was held and he was treated with antimicrobials. Hyperbaric oxygen was considered. However, he was deemed a poor candidate owing to his metastatic disease and emphysema, which would increase the risk of barotrauma. Furthermore, reconstructive surgery was not a viable option for the patient because of the presence of metastatic cancer. The patient eventually died from complications related to his metastatic cancer.

Case Discussion

Medication-related osteonecrosis of the jaw (MRONJ) was initially reported in 2003 in those who received zoledronate and pamidronate, both belonging to the class of bisphosphonates [2]. Since then, other drugs associated with MRONJ have been identified, including bevacizumab, with the first case reported in 2008 [1]. Upon PubMed search, we were able to count 29 reports of ONJ related to bevacizumab only, and 77 cases of bevacizumab with bisphosphonates as of May 22, 2023. Commonly used to prevent and treat osteoporosis, bisphosphonates are frequently used to reduce the morbidity in cancer patients with hypercalcemia of malignancy and bone metastasis [3].

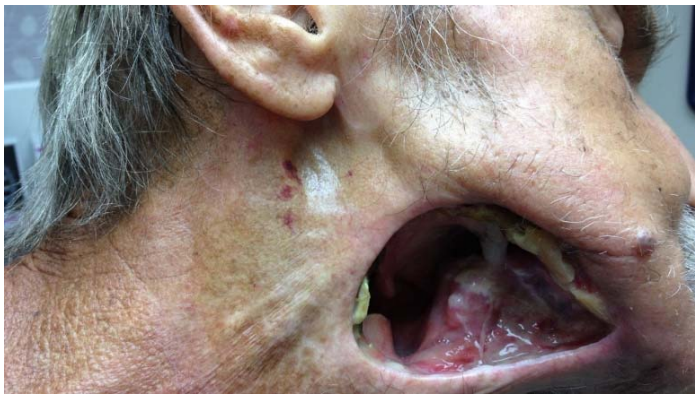

Figure 1. *Osteonecrosis of the jaw after radiation, followed by bevacizumab.*

According to a meta-analysis involving advanced breast cancer patients, the overall incidence of the jaw osteonecrosis was found to be 0.2% in patients treated with bevacizumab alone and 0.9% in those treated with the combination with bisphosphonates [4]. The MRONJ risk among cancer patients receiving antiresorptive or antiangiogenic agent is approximately 1% (range 0.2-6.7%). The risk of MRONJ is ten times higher in cancer patients compared to those receiving antiresorptive treatments for osteoporosis [5].

Other medications reported to be associated with ONJ include other anti-vascular endothelial growth factor agents, such as sunitinib and aflibercept, anti-receptor activator of nuclear factor kappa-B ligand (RANKL) antibody denosumab, lenalidomide, corticosteroid (prednisolone and dexamethasone), docetaxel, letrozole, methotrexate, everolimus, paclitaxel, imatinib, sorafenib, and nivolumab [6]. There are three case reports on ONJ associated with ipilimumab [7] and two case reports on pembrolizumab- related ONJ [8] as of May 22, 2023. The pathogenesis of MRONJ is considered multifactorial, including prolonged inhibition of bone turnover, infection, local trauma, and possibly impeded vascularization [6].

There is one published case report documenting ONJ after a combination treatment with irinotecan, fluorouracil, and aflibercept. However, the authors attributed the occurrence of ONJ to aflibercept, an anti-angiogenic agent, which has a known association with ONJ rather than irinotecan and fluorouracil [9]. In our patient's case, despite also receiving irinotecan and fluorouracil, we believe that the most likely cause of ONJ is bevacizumab.

Osteoradionecrosis is a complication that can occur following radiation, especially to the head and neck. In some cases, patients may experience exposed intraoral mandibular bone, which can lead to complications such as osteomyelitis and fractures of

the mandible [10]. Radiation therapy may trigger an excessive release of cytokines resulting in increased vascular permeability, localized edema, endothelial cell death, and vascular thrombosis, contributing to the development of osteoradionecrosis of the jaw [11]. Factors that increase the risk of osteoradionecrosis of the jaw include disease sites close to the mandible, a radiation dose of 80Gy or higher, and the presence of teeth [10].

Although the use of intensity-modulated radiation therapy has been associated with a lower incidence of ONJ, some patients will develop exposed intraoral mandibular bone. Many of these patients will go on to heal spontaneously and without complications. However, though many will heal spontaneously, others may develop osteomyelitis, fracture of the mandible, and soft tissue necrosis [12].

Our patient experienced initial damage to the mandible following intensity-modulated radiation therapy as evidenced by minimal fibrosis. The subsequent injury to the mandible may have been triggered by bevacizumab therapy.

Conclusion

Osteonecrosis of the jaw is a recognized complication associated with the use of bevacizumab, a VEGF inhibitor. Osteoradionecrosis is a late complication of radiation exposure, occurring when irradiated bone becomes devitalized [13]. Although there were no clear signs and symptoms of osteonecrosis before starting bevacizumab, our patient developed ONJ following the second cycle of bevacizumab. Being an anti-angiogenic agent, bevacizumab interferes with the vascularization in the jaw, impacting healing. Close monitoring, accompanied by thorough examination to detect early signs of osteonecrosis of the jaw, should be considered for patients who have undergone radiation therapy in the head and neck region and are receiving bevacizumab or other medications known to be associated with ONJ.

Potential conflicts of interest

The authors declare no conflicts of interest.

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