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# Osteonecrosis of the jaw with sunitinib and zoledronic acid combination: A case report

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Medication related osteonecrosis of the jaw (MRONJ) might lead morbidity that negatively affects the quality of life. MRONJ is mostly associated with antiresorptive bone treatments. Antiangiogenic treatments such as vascular endothelial growth factor (VEGF) targeted tyrosine kinase inhibitors also increase the risk of MRONJ, especially when combined with a bone-modifying agent (BMA). For the diagnosis of MRONJ; patient should have history of BMA or antiangiogenic treatments and no history of radiotherapy to jaw or metastasis.[1,2]

Anti-VEGF agents have been widely used in the last decade. Sunitinib is an oral, multi-targeted receptor tyrosine kinase inhibitor, which inhibits VEGF and several other tyrosine kinases. Sunitinib was approved by the FDA for the treatment of renal cell carcinoma (RCC), imatinib-resistant gastrointestinal stromal tumor and progressive, well-differentiated pancreatic neuroendocrine tumors.[3,4]

ONJ is commonly described with the use of antiresorptive agents. ONJ also described in a few cases in the literature with the use of tyrosine kinase inhibitors alone.[5–8] Thus it is assumed that concomitant use of antiresorptive agents and antiangiogenic therapies may increase the risk of ONJ.[9–14]

Here, we reported a patient with metastatic RCC who developed ONJ during zoledronic acid and sunitinib treatment.

## 1. Case

A 58-year-old patient who underwent left nephrectomy for renal cell carcinoma admitted to the medical oncology outpatient clinic for his treatment after the operation. Pathologic examination revealed clear cell renal cell carcinoma, the tumor was 10 cm diameter with no sarcomatoid differentiation, Fuhrman grade was 3, lymph nodes metastasis was also reported. Thoracal and abdominal computed tomography (CT) showed lung, lymph node, and sacral bone metastasis. The patient received palliative radiotherapy for sacral bone metastasis and interferon alfa treatment started because of health insurance coverage. Due to bone metastasis, intravenous zoledronic acid treatment also started and administered monthly. The patient was taking ibuprofen and controlled-release hydromorphone as painkillers. After 2 months interferon alpha switched to receive sunitinib 50 mg/day with four weeks on treatment and two weeks off (schedule 4/2) due to progression of lung metastasis on CT. While the patient was on sunitinib treatment, grade 2–3 mucositis and taste change complaints occurred. During drug holiday these complaints were resolved. After 6 cycles of sunitinib and 8 courses of zoledronic acid administration patient was admitted with pain and swelling of left mandible and difficulty of chewing. His oral examination revealed a lesion consistent with ONJ (shown in Fig. 1). Last zoledronic infusion was 3 months ago. Although the tooth in left mandible extracted totally, there was no recent tooth extraction history. Zoledronic acid and sunitinib treatment stopped, panoramic dental

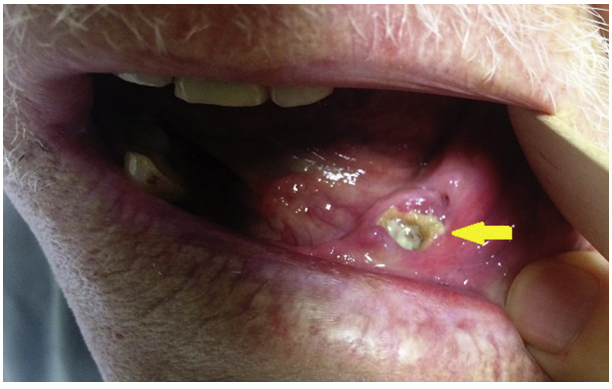

**Fig. 1.** Exposed necrotic bone in the left hemimandible.

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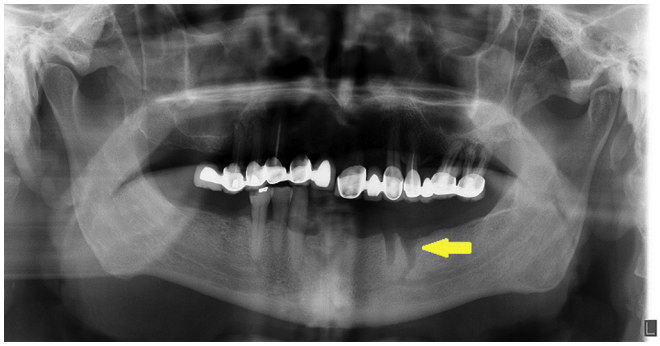

**Fig. 2.** Panoramic radiograph showing osteolytic lesions.

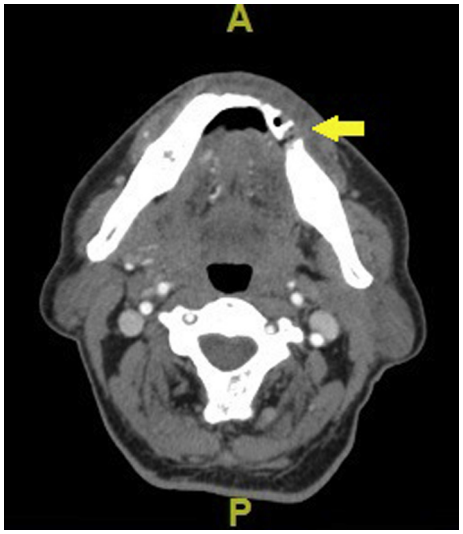


**Fig. 3.** Axial CT demonstrating MRONJ.

x-ray (shown in Fig. 2), mandibular CT (shown in Fig. 3) was obtained and the patient was referred to an oral and maxillofacial surgeon. After local treatment made by maxillofacial surgeon, the patient informed about his tumor burden, treatment options and side effects. The decision to continue treatment with sunitinib was made with the patient. Sunitinib treatment started again with 37.5 mg continuous daily dosing and zoledronic acid treatment discontinued. Until now, within 3 months after readministration of sunitinib, it was well tolerated.

## 2. Discussion

The pathophysiology of MRONJ is not clearly established. Proposed hypotheses are remodeling or oversupression of bone resorption, constant microtrauma, infection/inflammation and inhibition of blood supply; but all cases cannot be explained by these hypotheses.[15] It is shown in in vitro experiments that zoledronic acid inhibits angiogenesis with decreased circulating VEGF levels.[16,17] Also there is a growing evidence about the association between MRONJ and antiangiogenic tyrosine kinase inhibitors, especially with bevacizumab and sunitinib.[8,18–21] There have been multiple case reports of osteonecrosis of the jaw who are bisphosphonate naive.[5–8]

Combination of antiresorptive agents with antiangiogenic drugs raises the risk of MRONJ. In a study evaluating the incidence of ONJ with antiresorptive therapy, 5723 cancer patients enrolled, 89 (1.6%) patients were determined to have ONJ: 37 (1.3%) received zoledronic acid and 52 (1.8%) received denosumab.[22] In a retrospective review of 49 patients with advanced RCC who were treated with concomitant oral sunitinib or sorafenib and bisphosphonates, the incidence of ONJ was 10%.[22] In another report with 60 metastatic castration resistant prostate cancer patients, bevacizumab, docetaxel, thalidomide and prednisolone administered concurrent with zoledronic acid, 11 of patients (%18.3) developed ONJ.[23] The incidence of ONJ appears to be higher among patients who receive antiresorptive agents plus antiangiogenic agents.[9,10,20]

In our case, the patient was using both sunitinib and zoledronic acid. After 12 months of sunitinib administration ONJ developed. Our patient had intermittent mucositis in the oral cavity and his symptoms were resolving within 2 weeks breaks between sunitinib cycles. Overall stomatitis rate reported %47 in the safety study of sunitinib in patients with advanced RCC.[24] Although mucositis is one of the common adverse effect of sunitinib, mucositis may help us to estimate the patients who may develop ONJ. Hoefert et al.

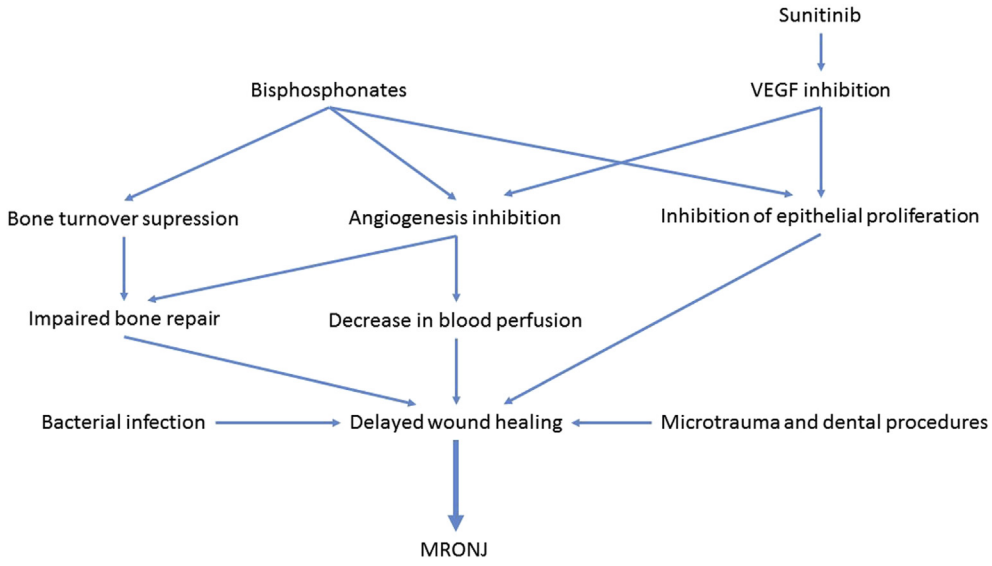


**Fig. 4.** Synergy between bisphosphonates and sunitinib.

reported an increased risk of MRONJ in patients with RCC and mucositis that treated with a combination of bisphosphonate and sunitinib.[18] Due to antiangiogenic effects of both sunitinib and zoledronic acid, a combination of these two drugs may maintain minimal mucosal lesions and impair wound healing. With the contribution of bad oral hygiene and inflammatory dental disease, MRONJ may emerge (Fig. 4).

As tumor progression may occur with sunitinib discontinuation, assesment and timely management of sunitinib releated toxicities are critical to ensure optimal treatment benefit. There is no standard guideline for the management of sunitinib side effects. Dosage or schedule modifications can be made.[25] Optimal dosing and scheduling of sunitinib has not been conclusively defined. Mostly used alternate dose regimens are 50 mg/day 2 weeks on 1 week off and 37.5 mg continuous daily dosing.

## 3. Conclusion

ONJ is a multifactorial process; impaired bone repair and angiogenesis, suppression of osteoclast activity, and local factors such as poor dental hygiene or dental extraction may be contributing to its development. The risk for ONJ may increase with the use of concomitant administration of antiresorptive agents and antiangiogenic therapies. To minimize the risk of ONJ especially when antiresorptive and antiangiogenic therapies are given together, dental examination and preventive dentistry procedures should be done before starting treatment.

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