Drug-induced osteonecrosis is a well-documented side effect of agents that have anti-angiogenic and anti-osteoclastic activity, for example bisphosphonates, bevacizumab and denosumab [1]. In many cases it is associated with dento-alveolar surgery, such as tooth extraction, placement of dental implants, etc. [2]. We present a rare case of osteonecrosis of the hard palate secondary to functional endoscopic sinus surgery and submucous resection.

**Patient Description**

A 63 year old man presented with the complaint of an air leak through his mouth to his nose. He had a known renal cell carcinoma, clear cell type, with metastasis to the lung and bones (left ileum and ribs). Following the initial diagnosis of renal cell carcinoma 3 years earlier, he underwent a right nephrectomy, and for 2½ years had been taking sunitinib and monthly pamidronate. While on this treatment, lesions developed on his lower and upper alveolar ridges after teeth extraction. At this point a functional endoscopic sinus surgery with submucous resection (FESS + SMR) was scheduled due to recurrent bleeding from a nasal polyp and sleep apnea. He discontinued the bisphosphonate treatment for 4 months before and a month after the operation, and the sunitinib treatment for 2 weeks before and after the operation.

A routine physical follow-up examination in the oncology department after the operation revealed an exposed necrotic bone in the central-posterior part of the hard palate, 3–5 mm in diameter with a communication to his nasal cavity, and three more lesions on his lower and upper alveolar ridges [Figure]. There was no sign of soft tissue infection around the oro-nasal fistula.

Positron emission tomography/computed tomography demonstrated local fluorine-18 absorption without fludeoxyglucose absorption, consistent with local bone remodeling without local infection or tumor. The lesions were diagnosed as osteonecrosis with a secondary oro-nasal fistula.

The patient was treated with antiseptic irrigation, conservative debridement, and antibiotics; the pamidronate and sunitinib treatments were discontinued. The fistula was obturated with a partial removable denture.

**Comment**

Bisphosphonates are analogues of pyrophosphate that affect bone remodeling by inactivation of the osteoclasts. The use of bisphosphonates has become an integral part of treatment for metastatic cancer to bones. Among the complications of bisphosphonate use is osteonecrosis of the jaw following dento-alveolar surgery. The common clinical presentation includes local pain, exposure of bony surfaces in the alveolar jaw bone, with progression to sequestrum formation and secondary local infection with local discharge and paraesthesia in some patients [3].

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**KEY WORDS:** osteonecrosis, bisphosphonate, functional endoscopic sinus surgery, submucous resection, sunitinib

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**Osteonecrosis of the maxilla (black arrow) and lesion in the palate (white arrow)**
The exact pathogenesis of osteonecrosis is unknown, although several explanations have been proposed [3], including disturbances in the normal remodeling of bone resulting in microdamage to the bone, and an ischemic effect that is related to the biphosphonate effect on vascular endothelial growth factor.

The current reported incidence rate ranges from 1.8% to 12.8% for intravenous bisphosphonates. Reported risk factors for the development of osteonecrosis include dento-alveolar surgery, time of exposure, type of bisphosphonate used, chemotherapy, radiotherapy to the head and neck, multiple myeloma or metastatic carcinoma to bones, diabetes mellitus, and corticosteroid therapy.

Several case reports have raised the possibility of increased risk for osteonecrosis in patients treated concomitantly with sunitinib [4]. Sunitinib inhibits several members of the tyrosine kinase receptor family, including vascular endothelial growth factor receptor, platelet-derived growth factor receptors (PDGFR and PDGFR-β), c-Kit and FLT3 and RET kinases. It is possible that the effect of sunitinib on those cytokines and its anti-angiogenicity exacerbated the osteonecrosis process.

The proposed management consists of meticulous oral hygiene, antiseptic irrigations, and systemic antibiotics when local infection is suspected. Local sequestrum debridement should be used conservatively with the aim of eliminating sharp bony edges. Nevertheless, none of these treatment modalities has proved successful in changing the clinical outcome. Cessation of bisphosphonate treatment after the development of osteonecrosis is recommended, but it does not have an impact on the necrotic process.

In most patients the bone defects are permanent. As such, prevention of this complication remains the main strategy – with dental procedures completed before initiation of the bisphosphonate treatment [3]. The benefit of a break in bisphosphonate treatment and the duration of this “washout period” is recognized with oral bisphosphonate treatment but is regarded as futile with the intravenous forms of bisphosphonate since these drugs remain in the bones for years. Therefore, the relative low risk of osteonecrosis should be weighed against the clinical implication of discontinuing this treatment.

Reports of osteonecrosis of the hard palate are sparse [5]. To the best of our knowledge this is the first published case of osteonecrosis of the hard palate related to functional endoscopic sinus surgery and submucous resection. Although osteonecrosis of the maxilla is well documented, it is usually limited to the alveolar ridge or wide processes that began at that site. In our patient there were four separate areas of osteonecrosis with no continuity between them. Bisphosphonate-induced osteonecrosis of the jaw is associated with local trauma. It is possible that local trauma to the bony structures triggered the clinical presentation in our patient.

A multidisciplinary approach is a major cornerstone in the treatment of the oncological patient. Coordination between the dental treatments and surgeries, with oncological chemotherapy radiotherapy and other oncological treatments such as bisphosphonate can decrease the risk of adverse outcomes.

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**References**


**Capsule**

**Opioids as long-lasting pain killers**
Opioids are among the most widely used and extensively studied drugs in the world. A continuous application of relatively low opioid doses is thought to be necessary to maintain synaptic depression in pain pathways. Dr.ia-Schutting and colleagues found that a single opioid application could produce lasting reversal of synaptic long-term potentiation in pain pathways. Chronic pain is often associated with synaptic potentiation in nociceptive pathways. A brief, high dose application of opioids depotentiated long-term potentiation in spinal pain pathways. The same dose also reversed hyperalgesia in behaving animals. Thus, opioids not only attenuate pain but may also eradicate a significant cause for chronic pain.

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**“Do not resent growing old. Many are denied the privilege”**
Irish proverb