

Medication-Related Osteonecrosis of the Jaw Associated with Pazopanib Monotherapy

Osteonecrosis de la Mandíbula Relacionada con Medicamentos Asociada con la Monoterapia con Pazopanib

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ABSTRACT: Pazopanib, an antiangiogenic agent, has shown promising results in controlling tumor growth and metastasis in patients with renal cell carcinoma. The use of pazopanib in the management of malignancies has increased over recent years, with more patients at risk of developing medication-related osteonecrosis of the jaw (MRONJ). This paper presents the first case report of MRONJ associated with pazopanib monotherapy. A 59-year-old man was referred to the dental clinic with complaints of dysphagia and dysgeusia. The patient was prescribed pazopanib (400 mg) daily following surgical treatment and chemotherapy for metastatic renal cell carcinoma. He had undergone extraction of the maxillary left second premolar nine weeks previously. Intraoral examination revealed exposed necrotic bone, which was treated effectively with leukocyte and platelet-rich fibrin (LPRF). The patient was followed up for 150 days after dental treatment with no signs of relapse.

KEY WORDS: osteonecrosis, jaws, pazopanib, oncology.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is characterized by an area of exposed jawbone that can be probed through an intraoral or extraoral fistula that has persisted for more than 8 weeks in individuals who have not undergone previous head and neck radiotherapy and who have received bisphosphonates, anti-resorptive agents or antiangiogenic drugs (Ruggiero *et al.*, 2014; Yarom *et al.*, 2019).

Pazopanib (Votrient®; GlaxoSmithKline, Brazil), an antiangiogenic agent, has shown long-lasting and beneficial antitumor effects in patients with advanced or metastatic renal cell carcinoma (Hutson *et al.*, 2010). It acts as an angiogenesis inhibitor, thereby preventing tumor growth and metastasis (Ruggiero *et al.*; Hutson *et al.*).

To the best of our knowledge, our search indicates that there has been only one case report of

Pazopanib-related MRONJ. However, the patient had concomitantly received treatment with the antiangiogenic agent, Everolimus (Afinitor®) (Jung, 2017). We aimed to describe the first case of MRONJ in a patient receiving Pazopanib monotherapy and the treatment and resolution of symptoms with leukocyte and platelet-rich fibrin membrane (LPRF).

CASE REPORT

A 59-year-old man was referred by the oncologist to the dental surgeon with complaints of dysphagia and dysgeusia. His medical history included the use of acetylsalicylic acid, levothyroxine sodium, megestrol acetate and codeine during pain episodes. He was diagnosed with renal cell carcinoma 3 years previously and was treated with radical nephrectomy (left side). Pulmonary and renal

metastases were observed within 1 year. Initially, the patient received oral chemotherapy with Temsirolimus (first-line) and Nivolumab (second-line), but without adequate response. Therefore, oral therapy with Pazopanib 800 mg (third-line) once daily was prescribed. Six months later, abnormalities in serum liver tests and hypothyroidism were detected. The oncologist adjusted the dose to 400 mg once daily to normalize liver and thyroid function. At three months following the initiation of therapy with Pazopanib (400 mg/day), the patient underwent a dental evaluation. In this moment, intraoral examination revealed localized periodontal disease with suppuration in the mandibular anterior region and exposed bone without suppurative changes in the maxillary left second premolar region, without periodontal disease in adjacent teeth. (Fig. 1A). The patient underwent extraction of the maxillary left second premolar approximately 10 weeks previously. The tomographic image (Cone-beam CT) showed diffuse hyperdense areas interspersed with hypodense areas near the alveolar ridge, suggestive of bone sequestration, and a non-healing extraction site in the maxillary left second premolar region (Fig. 1B). A presumptive diagnosis of Stage 1 MRONJ (Association of Oral and Maxillofacial Surgeons [AAOMS]) (Ruggiero *et al.*) was based on medical history, clinical examination, and tomography. The surgical approach involved the removal of necrotic bone and associated granulation tissue until bleeding from the underlying bone occurred. A leukocyte and platelet-rich fibrin membrane was applied, and primary closure was achieved with 4-0 nylon sutures (Fig. 2A). The patient was prescribed 0.12 % alcohol-free chlorhexidine mouthwash thrice daily, and amoxicillin 500 mg thrice

daily, for 7 days. Histopathological examination of the excised tissue revealed bone fragments with empty osteoclasts, medullary spaces filled by inflammatory cells with microbial biofilm, and areas of resorption peripherally. Surrounding the fragments, fibrous connective tissue with intense inflammatory cell infiltrate and stratified epithelial lining, sometimes in close contact with bone tissue, were observed. These aspects corroborated the final diagnosis of MRONJ.

In the 45-day postoperative period, we observed the presence of exposed bone in the same location (second upper left premolar) with purulent discharge through the gingival sulcus and no associated pain (Stage 2 AAOMS). The sequestered bone was removed and the site irrigated with copious amounts of 0.12 % alcohol-free chlorhexidine mouthwash. A combination of amoxicillin and clavulanate potassium was prescribed thrice daily for 14 days, with continued use of chlorhexidine mouthwash. At this point, the patient reported that the oncologist had adjusted the dose of Pazopanib to 600 mg/day for 15 days (i.e., 30 days after wound closure). Twenty days after the second surgery, the denuded region was covered with healthy gingival tissue with no signs of infection. The patient reported Pazopanib dose modification for the third time as hepatic alterations were observed at the dose of 600 mg/day. During the 150-day postoperative period, the surgical site showed the appearance of healthy gingival tissue, absence of edema, and no signs of bone infection or exposure. The patient was followed up with no evidence of recurrence or new episodes of MRONJ (Fig. 2B).

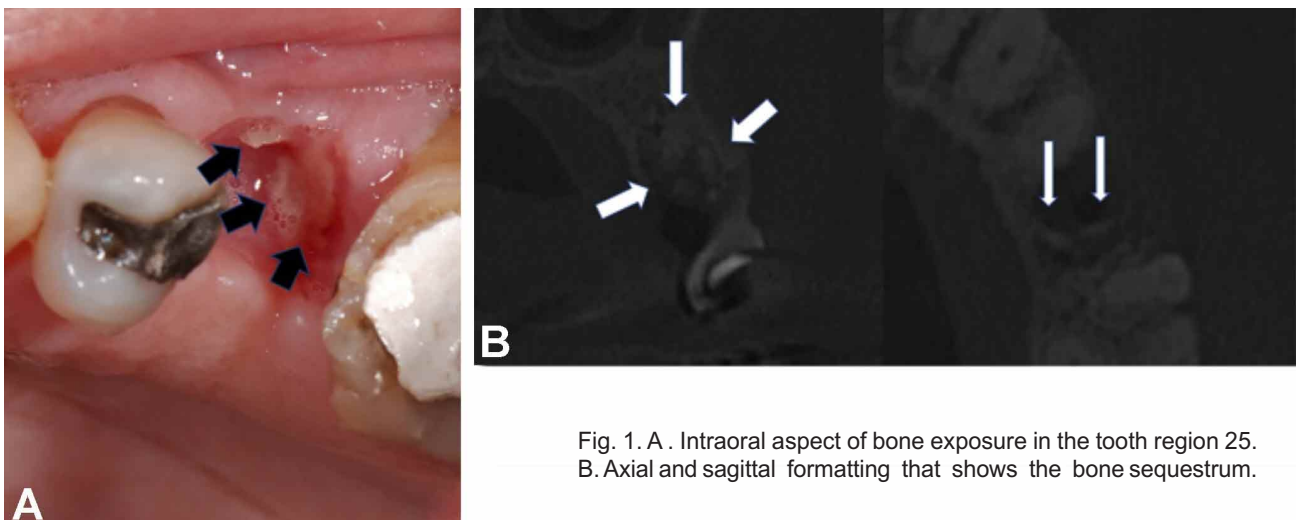


Fig. 1. A. Intraoral aspect of bone exposure in the tooth region 25. B. Axial and sagittal formatting that shows the bone sequestrum.

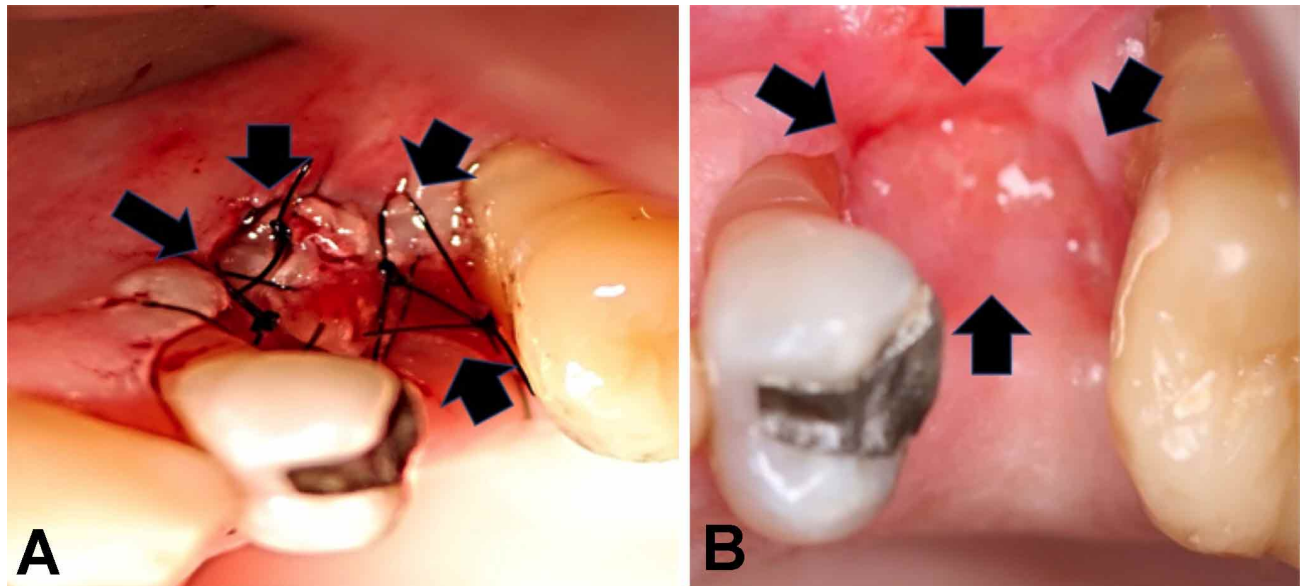


Fig. 2. A. Primary closure with nylon sutures (immediate postoperative). B. Postoperative period of 150 days control showing resolution of the bone exposition.

DISCUSSION

According to the AAOMS, the treatment of MRONJ should be based on the staging of the lesion (Ruggiero *et al.*). However, some lesions associated with MRONJ are refractory to conventional therapy. Hence, auxiliary approaches should be considered to improve treatment outcomes (Maluf *et al.*, 2018). LPRF is an autologous material that accelerates the angiogenesis and multiplication of fibroblasts and osteoblasts. The high concentration of growth factors present in platelets enhances the healing of soft and hard tissues. Moreover, it acts as a physical barrier, preventing secondary infections (Maluf *et al.*, 2016). Deregulated angiogenesis is directly related to tumor growth and invasion. Vascular endothelial growth factor (VEGF) represents one of the principal cytokines involved in the process of angiogenesis and bone repair and regeneration (Estilo *et al.*, 2008).

Pazopanib is an antiangiogenic tyrosine kinase inhibitor that acts by inhibiting VEGF and platelet-derived growth factor. Although Pazopanib is associated with adverse effects such as hepatotoxicity, hypertension, acts by thrombocytopenia, heart failure, fatigue, diarrhea, gastrointestinal perforation, it has shown a significant improvement in disease-free survival (Conley *et al.*, 2014).

There is no evidence in the literature that drug

holidays are effective in preventing MRONJ. However, AAOMS suggests the suspension of antiresorptive drugs for a period of 3 months (before and after) invasive procedures, in order to minimize the occurrence of MRONJ (Ruggiero *et al.*). Thus, it is suggested the condition of this patient has not been associated with the use of tivozanib, as this drug was used for a period of 8 months and suspended for a period longer than 2 years before the appearance of MRONJ. It is necessary that further studies be carried out to prove the effectiveness of the drug holiday.

The risk of developing MRONJ following tooth extraction is significantly higher in patients on VEGF inhibitors that alter bone metabolism (Gaudin *et al.*, 2015). Dental procedures such as extractions should be atraumatic with minimal manipulation of bone to minimize the need for bone remodeling, as these procedures are known to act as “triggers” for the occurrence of MRONJ (Ruggiero *et al.*; Gaudin *et al.*; Caminha *et al.*, 2019). Jung reported the case of a patient with renal cell carcinoma who had been treated with radical nephrectomy and pazopanib monotherapy for 6 months, followed by everolimus for 7 weeks. The patient developed MRONJ around implants placed 6 years previously. During the administration of Pazopanib, the patient remained asymptomatic. However, after the initiation of Everolimus therapy, she reported pain, gingival bleeding, and purulent discharge. Thus, it can be assumed that Everolimus potentiated the action of Pazopanib, leading to

osteonecrosis. To date, there are no reports of MRONJ associated with Pazopanib monotherapy in the literature.

Patients scheduled to undergo antiangiogenic therapy should receive a comprehensive dental evaluation before initiating treatment. The treatment plan should ensure that the necessary dental procedures are performed to eliminate the foci of infection, such as periodontal therapies and extractions, to reduce the risk of developing MRONJ.

CONCLUSION

It is essential that multidisciplinary teams, working in the oncology area, are aware of the possibility of osteonecrosis of the jaws associated with monotherapy with Pazopanib.

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RESUMEN: Pazopanib, un agente antiangiogénico, ha mostrado resultados prometedores en el control del crecimiento tumoral y las metástasis en pacientes con carcinoma de células renales. El uso de pazopanib en el tratamiento de las neoplasias malignas ha aumentado en los últimos años, con más pacientes en riesgo de desarrollar osteonecrosis de la mandíbula relacionada con la medicación (MRONJ). Este artículo presenta el primer reporte de caso de MRONJ asociado con la monoterapia con pazopanib. Un hombre de 59 años fue remitido a la clínica dental con quejas de disfagia y disgeusia. Al paciente se le prescribió pazopanib (400 mg) al día tras tratamiento quirúrgico y quimioterapia por carcinoma metastásico de células renales. Había sido sometido a extracción del segundo premolar superior izquierdo nueve semanas antes. El examen intraoral

reveló hueso necrótico expuesto, que fue tratado eficazmente con leucocitos y fibrina rica en plaquetas (LPRF). El paciente fue seguido durante 150 días después del tratamiento dental sin signos de recidiva.

PALABRAS CLAVE: osteonecrosis, mandíbulas, pazopanib, oncología.

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