Osteonecrosis of the jaw associated with imatinib therapy in myeloproliferative neoplasm: a rare case report

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Medication-related osteonecrosis of the jaw (MRONJ) is a relatively infrequent but very well-known adverse effect of bisphosphonates. This rare complication of bisphosphonates is rarest with the use of certain drugs. Tyrosine kinase inhibitors (TKIs), particularly used in renal cell carcinoma or gastrointestinal tumors as a chemotherapeutic agent, can precipitate this particular medical condition of bone when it is associated with either radiation or bisphosphonates, though, monodrug therapy with TKIs rarely causes MRONJ. This article describes a rare case of necrosis of the jawbone in a patient with a myeloproliferative neoplasm who was receiving the TKI imatinib and had no history of bisphosphonate or radiation therapy to head and neck region. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:e157–e162)

Medication-related osteonecrosis of the jaw (MRONJ) is defined as exposed bone or bone that can be probed through an intraoral or external fistula in the maxillofacial region, that does not heal within 8 weeks, and that occurs in a patient who has received a bone-modifying agent or an angiogenic inhibitor agent with no history of head and neck radiation.[1,2] This particular medical condition is commonly associated with use of bisphosphonates (BPs) and was termed "bisphosphonate related osteonecrosis of jaws" (BRONJ) by Marx in 2003.[3] In the past few years, diagnosing cases of osteonecrosis of the jaws that were related to other classes of drugs changed the term from BRONJ to MRONJ.[4] The prevalence of MRONJ is relatively low in patients who receive BP therapy. The prevalence reported by Lo et al[5] in 2010 was 0.10% in patients with exposure to BPs. The prevalence of MRONJ in patients who were receiving antiresorptive therapy was reported by Rugani et al[6] in 2016, with prevalence in breast cancer being 2.09%, that in prostate cancer being 3.8%, and that in multiple myeloma cases being 5.16%.

Local trauma in either soft or hard tissues is known to cause MRONJ. Local trauma in the form of dental extractions (45%) is considered the most common triggering factor in the development of osteonecrosis, and the second most common factor that can precipitate MRONJ is periodontal infections (10%).[7,8]

Other oral risk factors that can also be associated with MRONJ are invasive procedures such as implant placement and sore spots due to ill-fitting dentures.[8-10] Patients who are receiving corticosteroids and have other comorbidities, such as diabetes mellitus, renal failure, and medical conditions, such as anemia and osteoporosis,[11] have increased risk of developing MRONJ. Poor oral hygiene and smoking are the other precipitating factors that can also increase the risk of MRONJ.[8,12] Dental surgeons play a crucial role in identifying the early signs of MRONJ. For the prevention of this unwanted complication, dental surgeons should carefully examine patients who are receiving BP therapy or any other drug therapy that can cause MRONJ.

Medications responsible for the development of MRONJ are antiresorptive (including BPs and receptor activator of nuclear factor κB ligand inhibitors), antiangiogenic factors, human monoclonal antibodies, and tyrosine kinase inhibitors (TKIs). TKIs are one of the drug categories generally used in renal cell carcinoma, gastrointestinal carcinoma, chronic myeloid leukemia (CML), and lymphoblastic leukemias.[13-15] Recently, imatinib has been reported to cause MRONJ[14]; however, the occurrence of MRONJ with this particular drug is very rare. This article presents a rare case of MRONJ that developed after imatinib therapy in a patient with a myeloproliferative neoplasm with hypereosinophilia.

CASE REPORT

Medical history

A 49-year-old man reported to Homi Bhabha Cancer Hospital, Varanasi, India, with the chief complaint of weakness in his legs of 1 month's duration. He was completely paraplegic within the next 20 days. Upon investigation, unusual hypereosinophilia and leukocytosis were noted. Magnetic resonance imagining (MRI) of spinal cord showed multilevel infiltrative disease with cord compression. MRI of brain revealed the right frontal lobe with transosseous extension into the scalp, leading to multilevel compressive myelopathies

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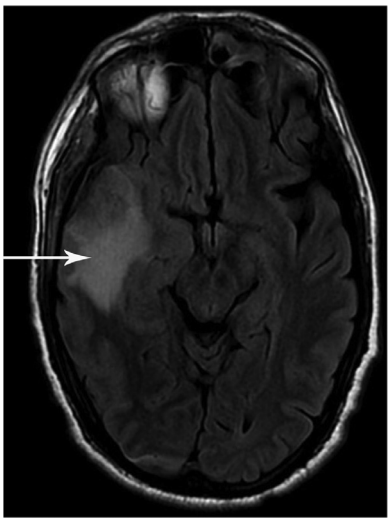

Fig. 1. Transverse section of magnetic resonance imaging of the brain demonstrating right frontal lobe and transosseous compression.

(Figure 1). On the basis of these initial investigations, a differential diagnosis of Langerhans cell histiocytosis (LCH) was reported by the clinical team.

Further investigation showed high levels of immunoglobulin E and mild elevation of serum tryptase. Upon direct harvesting of a bone marrow aspirate, fluorescence *in situ* hybridization performed on interphase and metaphase cells showed cysteine-rich hydrophobic domain 2 (CHIC2) locus deletion in 30% of cells with FIP1-like/platelet-derived growth factor receptor α (FIP1 L1-PDGFRA) translocation, which changed the diagnosis from LCH to myeloproliferative neoplasm with hypereosinophilia. FIP1 L1-PDGFRA is a novel therapeutic target of the TKI imatinib, which provides the basis for the treatment of these patients with this drug.[16,17] With all these findings, the patient was prescribed imatinib 600 mg once daily on August 19, 2019. Upon improvement of symptoms after 1 month, the dose of imatinib was reduced to 400 mg once daily. Upon further improvement, the dose was reduced to 200 mg once daily after 1 month, and the patient has been maintained on that same drug dose.

Dental history and MRONJ

The patient visited the dental clinic on October 3, 2019, with the chief complaint of altered sensation in the right lower posterior region of his jaw for the past 2.5 years. He also gave a history of extraction of teeth from the same site. He was not able to correlate the date of extraction with the initiation of imatinib. He did not have any past history related to BP and radiation therapy.

The patient had visited a local dental surgeon and was advised to undergo extraction of the periodontally compromised teeth in the mandibular right posterior quadrant, though his past history was not taken into consideration. After the extractions, in view of the long period of unhealed socket and due to worsening of his oral conditions, the patient was advised to consult an oncologist for the unhealed socket. The patient was referred to the hospital dental department by the medical oncologist for further evaluation of the unhealed socket.

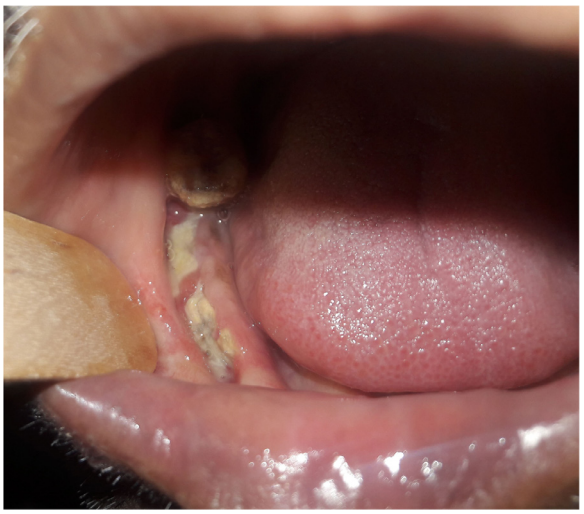

Fig. 2. Intraoral clinical appearance of necrotic bone.

Upon clinical examination, there was evident exposed bone in the right lower quadrant intraorally in relation to the second premolar, first molar, and second molar (Figure 2). The initial examination revealed no pain, pus discharge, or evident inflammation intraorally or extraorally in the affected area. With previous cone beam computed tomography (CBCT) and radiologic reports (Figures 3 and 4) and the existent clinical situation, a diagnosis of stage 1 MRONJ was formulated

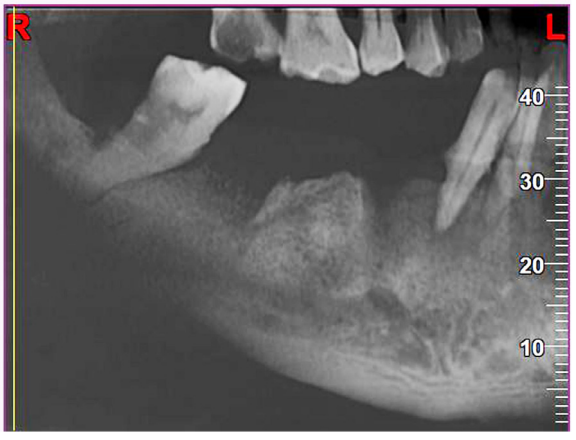

Fig. 3. Radiographic picture showing unhealed socket and necrotic bone.

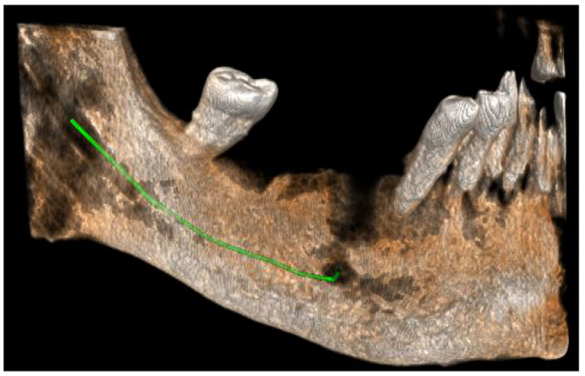

Fig. 4. 3-Dimensional computed tomographic scan showing area of necrotic bone.

according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) classification.[1]

TREATMENT

The treatment regimen was started as suggested by the AAOMS protocol.[18] The patient was advised on meticulous oral hygiene with the use of oral rinse of povidone iodine and was kept on an antimicrobial agent (amoxicillin plus clavulanic acid 625 mg twice daily) for 7 days. Along with the oral rinse of povidone iodine, he was kept on oxum spray, a superoxide oxygen spray (Alkem Laboratories Ltd, Mumbai, India), which is a proven effective medication in wound healing.[19-21] A pentoxifylline and tocopherol regimen was also added to prevent further progression of MRONJ.[22] The patient was called for the next follow-up after 8 weeks as per the latest Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology/American Society of Clinical Oncology (MASCC/ISOO/ASCO) clinical practice guideline.[23]

At his first follow-up visit, the patient was comfortable and managing his routine activities well. He was advised to maintain oral hygiene and to attend follow-up every 2 months to evaluate progression of the MRONJ lesion.

In the second follow-up visit after 2 months, he complained of paresthesia in the right half of his lower lip. On the basis of this complaint, a fresh CBCT of the mandible was performed to evaluate the progression of the disease. Meanwhile, the treating medical oncologist was consulted for opinion on discontinuation of the drug or a drug holiday for at least 2 to 3 months to prevent the progression of the condition. Because the disease is correlated with FIP1 L1-PDGFRA translocation, where imatinib, being the drug of choice, was necessary for the prevention of the disease progression, a drug holiday was not advisable in this patient.

CBCT of the patient's mandible revealed that the necrosis of bone had increased compared with the previous imaging report, with symptoms of paresthesia

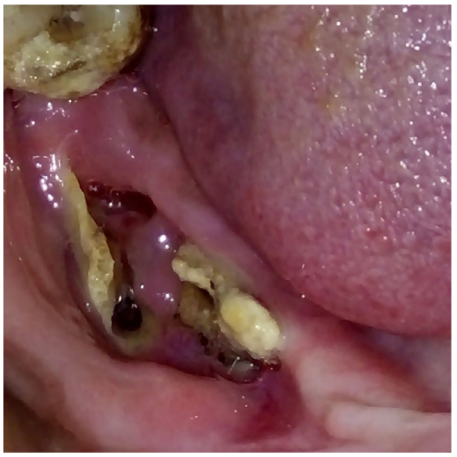

Fig. 5. Clinical picture of progression of the disease.

and mild pain. The staging of MRONJ progressed from stage I to stage II (Figure 5 and 6). The cure of the primary disease depended on imatinib; hence, a drug holiday was not possible. Surgical removal of the necrotic bone tissue and filling the defect with plasma-rich fibrin (PRF) was not indicated.

On the basis of clinical findings and progression of the disease, it was advised to start antimicrobial therapy to prevent the further progression of necrosis. According to previous literature, a combination of amoxicillin/ampicillin plus clavulanic acid and doxycycline has shown promising results in the healing of osteonecrosis of the jaw.[18,24-28] The patient was advised to continue the suggested conservative medical management with maintenance of meticulous oral hygiene and report to the department for regular follow-up after 2 months. On the basis of the MASCC/ISOO/ASCO clinical practice guideline,[23] the patient had clinically stable mucosal coverage (mild improvement; 50% of mucosal coverage); the symptoms of halitosis and pain were resolved; the signs of infection and inflammation were resolved; and radiographically the lesion was stable. At his next follow-up visit, the patient's clinical condition and quality of life were

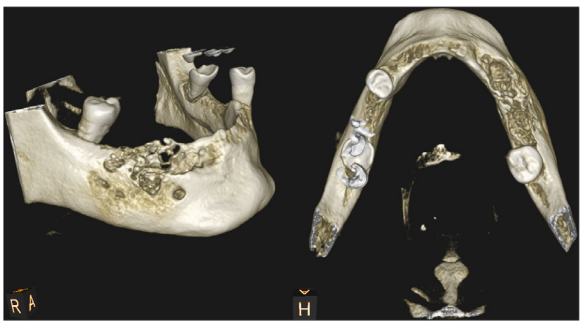

Fig. 6. 3-Dimensional computed tomographic lateral and occlusal views showing progression of necrotic bone.

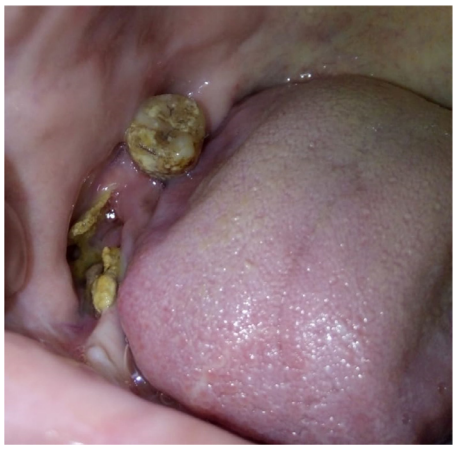

Fig. 7. Clinical follow-up image showing marked improvement after antimicrobial therapy.

improved (Figure 7). The patient has been advised to maintain good oral hygiene and visit the department every 2 months for follow-up and evaluation.

DISCUSSION

In the past few years, the number of patients developing MRONJ is increasingly associated with TKIs. Most of the cases of MRONJ associated with TKIs are reported with the drug sunitinib.[29-31] Other than sunitinib, there are other TKIs that have been reported to cause MRONJ. Cabozantinib, used in medullary thyroid carcinoma, has been reported to cause MRONJ in a short period of time: within 3 to 6 months.[32,33] Sorafenib and dasatinib have also been reported to cause MRONJ in metastatic hepatocellular carcinoma and acute lymphoblastic leukemia, respectively.[34,35] Patients receiving combination therapy with TKIs and other bone resorption factors/bone-modifying agents have a 5-10 times higher risk of developing MRONJ than patients receiving bone-modifying agents only.[10]

Imatinib is one of the TKIs that is rarely associated with osteonecrosis of the jaw. Imatinib mesylate (IM) is a competitive TKI commonly used for treatment of CML. It has also proved to be efficient in the treatment of advanced gastrointestinal stromal tumors, c-KIT mastocytosis, and myeloproliferative disorders with rearrangement of the platelet-derived growth factor receptor (PDGFR) gene.[13]

In malignancies other than CML, IM inhibits the tyrosine kinase domains of KIT and PDGFRα/β. Myeloproliferative disorders with PDGFR rearrangement show great sensitivity to IM and mostly require a lower dose of IM. This is especially true of chronic eosinophilic leukemia, which involves a fusion transcript of FIP1-like 1 and PDGFRA.[36] *In the present case of myeloproliferative neoplasm with* hypereosinophilia and FIP1 L1-PDGFRA translocation, imatinib was started at a lower dose of 600 mg, which was tapered to 200 mg once daily. The clinical picture subsequent to tooth removal before or after the imatinib therapy included bone sequestration, intraoral/extraoral inflammation, halitosis, and paresthesia of the lower lip. The clinical signs and symptoms resembled osteonecrosis of the jaw related to BP use. Although the patient had never received any BPs and had not undergone radiation therapy of the head and neck region, stage I/II of MRONJ in this case was related to imatinib, a TKI.

Reports in the literature reveal very few cases of osteonecrosis of the jaw related to imatinib, either alone or in combination with BPs.[14,37] Surprisingly, one case of tibial fracture was also reported in the literature, which showed the effect of imatinib on peripheral bones.[38] The mechanism of action of the osteonecrosis of bone is not fully elucidated; nevertheless, there are various articles in the literature that have hypothesized that IM is responsible for alteration in bone remodeling.[39-41]

According to Delanian,[42] pentoxifylline has shown improved peripheral blood flow and microcirculation with increasing tissue oxygenation to the cells. In addition, pentoxifylline has anti−tumor necrosis factor α effect and has also shown fibrosis inhibition and enhancement of collagen activity.[43] The antioxidant property of tocopherol or vitamin E, along with the benefits of enhancing wound healing by weakening tissue fibrosis and reducing the damage caused by free radicals impacting necrosis, has shown promising results in cases of osteonecrosis.[44] In view of all these advantages, addition of pentoxifylline and tocopherol in the treatment regimen is considered to be effective in the treatment of MRONJ.[22,45,46] However, as reported by Heifetz-Li et al,[47] currently there is no consensus available to prove the efficacy of this treatment regimen. Nevertheless, Heifetz-Li et al[47] stated that this regimen is as effective as the other nonsurgical treatment modalities. Surgical intervention with PRF is considered to be an effective treatment option to treat MRONJ associated with BPs.[48,49] According to Bilimoria et al,[50] minimally invasive surgeries with a piezoelectric method and placement of PRF in the affected area after debridement have shown better prognosis than extensive surgeries. Generally, we follow a drug holiday of 2 to 3 months before and after surgical interventions as a preventive protocol to reduce the chances of MRONJ progression because of surgical manipulation. However, in this case, surgical intervention was not undertaken, because the necessity of imatinib was inevitable due to its requirement for treatment of the primary disease. For the same reason, no drug holiday was provided to the patient for any surgical intervention, mainly debridement and PRF treatment. A drug holiday definitely is an ongoing controversial area, and various papers have been published regarding drug holidays with BPs,[8,51,52] although, to our knowledge, no such data are available for the TKI imatinib. Our patient was counseled

and encouraged to use povidone iodine mouthwash to maintain good oral hygiene, along with other necessary medications (oxum spray, pentoxifylline, and tocopherol regimen), to prevent progression and to keep regular follow up with the dental department for evaluation.

CONCLUSION

FIP1 L1-PDGFRA is a novel therapeutic target for imatinib therapy, particularly in conditions such as myeloproliferative neoplasms. However, oral complications such as osteonecrosis should be considered during imatinib therapy. Careful monitoring of oral conditions with regular follow-up visits can help in preventing progression. In the literature, very few cases of MRONJ related to imatinib have been reported; nevertheless, it will be beneficial to substantiate this medical condition with future research and studies.

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