

Peer Review File

Article information: <https://dx.doi.org/10.21037/tcr-21-404>

Reviewer A

This manuscript aims to describe a case of osteonecrosis of the maxilla associated with an unexpected bleed. While this appears to a novel finding I have concerns with the limited diagnostic impression provided in the manuscript, specifically in reference to the excessive bleeding. My other comments are as follows:

1. The title states that this is a literature review and a case report but there is no literature review provided. If the authors are referencing to their discussion section as the literature review, it should be modified and presented as a separate section. More importantly, what is the focus of the literature review? The discussion section leaps from clinical to molecular information about MRONJ without any specific focus of review.

Reply1: We deleted the “literature review” in the title. Besides, we summarized ONJ related to bisphosphonate therapy in cancer patients in previous studies and supplemented table 1.

In the discussion part, we focus on the noteworthy findings of this case. First, the combined use of NBP and angiogenetic drugs is rather common in clinical practice, but the following disastrous complication such as osteonecrosis occurred in our patient fails to attract enough attention. We should figure out the high-risk population of osteonecrosis, adjust the intensity of treatment and duration correspondingly and avoid severe side effects to the greatest extent. Thorough oral inspection should be done before using BP or anti-angiogenesis drugs and unnecessary oral procedures should be avoided during treatment. Second, we have analyzed the mechanism of osteonecrosis induced by NBP and angiogenetic agents. In the future, novel drugs targeting the key link in the osteonecrosis development should be addressed to change the therapeutic dilemma of osteonecrosis now. Third, care needs to be taken to ensure that osteonecrosis is not mistakenly diagnosed as BM in heavily-treated cancer patients. Pathology is essential to ensuring the correct diagnosis and management.

Changes in the text:

We deleted the “literature review” in the title. (Page 1, line 1-2).

We summarized ONJ related to bisphosphonate therapy in cancer patients in previous studies and supplemented table 1. (Page 8, line 154-155, highlighted light gray part; Page 13-14, Table 1).

We focused on the noteworthy findings, namely taking home messages. (Page 11-12, line 229-243, highlighted light gray part)

2. What is the reference to Figure 4? Figures should be presented in the case report section and not in the discussion. Did the authors create this mechanism of ORN using their literature review? If yes, it should be presented as a separate manuscript at least with results from a systematic literature search that enabled authors to create this.

Reply 2: We only submitted 3 figures. Figure 3 described the complicated molecular mechanism of ONJ. Because it is a case report, there is no need to describe all the molecular mechanisms of medications. We deleted Figure 3. In the revised version, we made the molecular mechanism of ONJ resulted from antiresorptive and antiangiogenetic agents concise.

Changes in the text:

Figure 3 was deleted.

The underlying mechanism of ONJ resulted from antiresorptive and antiangiogenetic agents was presented concisely and clearly. (Page 10, line 189-205; Page 11, line 215-216; highlighted dark gray part)

3. Figure 1 and 3 should be deleted. Figure 2 should be enlarged.

Reply 3: We only submitted 3 figures. Figure 3 described the complicated molecular mechanism of ONJ. Because it is a case report, there is no need to describe all the molecular mechanisms of medications. We deleted Figure 3.

Figure 1 A-C (typical slices of maxillofacial CT) demonstrated severe destruction and loss of right maxillary bone, maxillary sinus medial and lateral wall. Figure 1 D (the pathology of the exfoliated bone tissue) showed no osteocytes in the lacunae, indicating bone necrosis. Therefore, we think Figure 1 should be presented. Figure 2 was the timeline of diagnosis, treatment and follow-up. The patient died in July 24th, 2020. We updated the follow-up and Figure 2.

Changes in the text:

Figure 3 was deleted. Figure 2 was updated.

4. The case report should describe the diagnostic impression in more details specifically pertaining to osteonecrosis and the bleed, in addition to the medical and oncologic history of the patient. With the current information provided, the diagnosis of ORN related bleeding is not convincing. What was the differential diagnoses? If pathology was only done was exfoliated bone rather than a proper biopsy, then the diagnoses could be misleading. Additionally, what was the source of the bleeding? Was it an artery? Was it bone related bleeding? What was the embolization done for? Inadequate information is provided about the case.

Reply 4:

(1) Diagnosis: We provide the CT scan images of the maxillofacial region and the pathological biopsy results of the exfoliated bone tissue. (See Figure1)

(2) Differential diagnosis: Our patient was differentiated from bone metastasis,

suppurative osteomyelitis and radiation osteomyelitis. The patient had no obvious symptoms such as high fever and chills and the results of laboratory examination excluded suppurative osteomyelitis. Radiation osteomyelitis was excluded in the patient because there was no history of radiotherapy in the maxillofacial region. Pathological biopsy of exfoliated bone tissue showed necrotic bone tissue and no malignant tumor infiltration.

(3) The purpose of interventional embolization: The bleeding still continued despite of medical hemostasis and packing therapy. In order to prevent shock caused by further bleeding, interventional embolization was recommended to stop bleeding.

(4) Intraoperative arteriography revealed the presence of contrast agent dispersion from the upper alveolar branch of the right internal mandibular artery, which confirmed that the hemorrhage was caused by the artery. The bleeding was stopped after embolization of the internal maxillary artery, so the bleeding caused by arterial invasion in the area of osteonecrosis.

Changes in the text:

We supplemented the differential diagnosis part. (Page 8-9, line 164-172, highlighted light blue part)

We added more details and adequate information of this case. (Page 6, line 121-126, highlighted light blue part)

Reviewer B

Initially I would like to congratulate the authors for the reported case. The occurrence of osteonecrosis in the sinus region is not frequently reported and the case brings an important alert.

However, I would like to make some comments in order to help improve the manuscript to make it clearer.

The authors describe in detail the entire evolution of the patient, but it provides little information about how osteonecrosis was treated. They also mention a situation of toothache, but do not delve into the issue and the possibility of any relationship.

In the discussion, I believe that because it is a case report, there is no need to describe all the molecular mechanisms of medications. It would be more interesting to address the clinical aspects, treatment and associated complications.

Figures 1 and 4 are unnecessary.

Some corrections in English are also needed.

Reply1:

--The bleeding was stopped after interventional embolization. Anti-infective treatment was given. We supplemented the details of interventional embolization. Because of the massive defect caused by ONJ, operation was impossible for ONJ.

Changes in the text:

We added more details and adequate information of this case. (Page 6, line 121-126,

highlighted light blue part)

We added the treatment choice of ONJ in this patient. Because of the massive defect caused by ONJ, operation was impossible for ONJ. (Page 11, line 222-225, highlighted light green part)

-- Despite of no prior tooth extraction, the history of oral infection in our patient partly aggravated the process of osteonecrosis. Lipopolysaccharide, a bacterial cell wall constituent, was documented to enhance the direct necrotic effects by ZA. Over 800 kinds of bacteria inhabit the human oral mucosa. When there is oral mucosal damage, these bacteria easily reach the jaw bones and participate in bone necrosis. We supplemented the related analysis about the situation of toothache and ONJ.

Changes in the text: We delve into the relationship between the situation of toothache and ONJ. (Page 9, line 183-188, highlighted yellow part)

--This is a case report, so there is indeed no need to describe the complicated molecular mechanism of ONJ. We only submitted 3 figures. Figure 3 described the complicated molecular mechanism of ONJ. We deleted Figure 3. In the revised version, we made the molecular mechanism of ONJ resulted from antiresorptive and antiangiogenic agents concise. Figure 1 A-C (typical slices of maxillofacial CT) demonstrated severe destruction and loss of right maxillary bone, maxillary sinus medial and lateral wall. Figure 1 D (the pathology of the exfoliated bone tissue) showed no osteocytes in the lacunae, indicating bone necrosis. Therefore, we think Figure 1 should be presented.

Changes in the text:

Figure 3 was deleted.

The underlying mechanism of ONJ resulted from antiresorptive and antiangiogenic agents was presented concisely and clearly. (Page 10, line 189-205; Page 11, line 215-216; highlighted dark gray part)

-- Our manuscript has been edited for correct English language usage, grammar, punctuation and spelling by qualified native English-speaking editors at AME Editing Service. We can provide the related certificate for editorial review.

Changes in the text: The revised manuscript has been edited by English Language Editors: L. Huleatt and J. Gray at AME Editing Service.