

Dear Editor and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Reduced delay in the diagnosis of keratocystic odontogenic tumor with malignant transformation: a case report" (Manuscript NO.: 54157). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer's comments are as follows:

Reviewer #1: Title: The nomenclature of 'KCOT' was changed to Odontogenic Keratocyst in the last WHO consensus. KCOT should be changed as OD in the title and throughout the text. Abstract: Line 24-25: The clinical and radiographic data are needed to diagnose the case as KCOT. Radiographic data about the case should be presented in this section. Discussion: In the last paragraph, the information about treatment is unnecessary. The summary paragraph should be concise and comprise the main idea of the manuscript.

1. Response to comment:

Thanks for your comments, the responds are as follows:

- i) KCOT is replaced by odontogenic keratocyst (OD) in this manuscript.
- ii) Information of radiographic results is added in abstract (page 2, line 33-35): Cone beam computed tomography revealed a cystic lesion with massive bone destruction from the left maxillary central incisor to the left secondary maxillary premolar and local bony destruction in the left first mandibular molar.
- iii) we delete information of treatment and re-summarize this case (page 9, line 179-183): In summary, this article presents a case with reduced delay in the diagnosis of PIOSCC in the maxilla. Our case suggests that for the timely diagnosis and treatment of PIOSCC, clinicians should be aware of the malignant transformation of OD, especially when patients present a cystic lesion with a long history, chronic inflammation, recent aggravated behaviors including pain, and lymph node enlargement.

Reviewer #2: Specific Comments to Authors: The case report "Reduced delay in the

diagnosis of keratocystic odontogenic tumor with malignant transformation: a case report” mainly focused on PIOSCC, which was transformed from KCOT in rare cases. In this report, the authors report a case of malignancy derived from KCOT with five days-delay in diagnosis to take a closer look at PIOSCC. However, Authors must understand that a case report is not the one which highlights a rare condition but the one that has a clear message that can be generalized, and is relevant to many other clinicians. It is a topic of interest to the researchers in the related areas but the paper needs very significant improvement before acceptance for publication. My detailed comments are as follows: 1. On the section of Imaging examinations, too few description about images is given here. Instead, the authors may provide more accurate description about images. 2. As the key to the diagnosis of PIOSCC, the description of pathological features in this part is not detailed enough. 3. Most of the content on Discussion section is similar to that on Introduction section, without in-depth discussion of the cases, KCOT or PIOSCC. Here the authors should give information about the condition or intervention in question, such as the basic epidemiology, pathophysiology, clinical presentation, investigations, and treatment. It is extremely important for authors to show how your case differed from the norm and how this is contributing to medical understanding.

2. Response to comment:

It is really true as Reviewer suggested these defects exist in the previous manuscript, our responds are as follows:

i) Detailed information of CT results is added in the revised manuscript (page 6, line 113-118): **Fig. 1:** A: Panoramic radiographs revealed a cystic lesion in the left maxilla and periapical radiolucency of inflammatory origin in the left first mandibular molar. The left maxillary lesion extended from the left maxillary central incisor to the left secondary maxillary premolar and showed no evident root resorption. B–D: An axial scan revealed buccal and palatal swelling of the cystic lesion with a clear boundary and a palatal cortex defect. E: Three-dimensional imaging revealed an intact labial maxillary bone.

ii) the detailed pathological features is provide in the revised manuscript (page 7, line 125-128): **Fig. 2:** Malignant transformation of ODs. Histopathological examination revealed an intact structure of cyst lining (A, $\times 40$) and inflammatory cell infiltration in submucosa (B, $\times 100$); C: destruction of cyst lining and invasion of massive squamous cell carcinoma ($\times 40$); D: moderately differentiated squamous cell carcinoma (distinct foci of squamous cell carcinoma, $\times 100$).

iii) As the reviewer suggested, we provide more information about OD with malignant transformation in discussion (page 8, line 140-143; line 152-154): Primary intraosseous squamous cell carcinoma (PIOSCC) is classified into three types: i) a solid cancer invades marrow spaces and incudes osseous reabsorption; ii) a squamous cell carcinoma derives from an odontogenic cyst; iii) a squamous cell carcinoma derives from other benign epithelial odontogenic tumors...In conjunction with the patient's medical history, recently aggressive behavior, and intraoperative findings, we considered that the patient suffered from PIOSCC deriving from OD.

We subsequently discuss commonalities among cases with a prejudged possibility of a malignant tumor, and commonalities among cases with delayed diagnosis (page 8 and 9, line 155-178):

Although information about biological characteristics of malignant OD is rare, the high recurrence rate and poor survival of PIOSCC may be partly attributed to its misdiagnosis as OD; subsequent curettage is conventionally performed, followed by enucleation combined with peripheral ostectomy and radical resection for localized and large or ill-defined lesions, respectively¹². Apart from the similarity of clinical behavior and radiologic examination results between PIOSCC and OD, the acquired malignant transformation of OD as confirmed by pathology is another huge barrier to prescribing the proper treatment of patients with PIOSCC. Although the malignant lesion was diagnosed by enucleation in this case, biopsy and enucleation are associated with the misdiagnosis of PIOSCC in previous reports^{5,6}. More information is required to assess malignant tumors before the identification of the characteristics of malignant transformation of OD.

A literature review suggests several cases of PIOSCC were diagnosed via surgical

biopsy because of a prejudged possibility of a malignant tumor, several cases were unsuspectedly diagnosed by enucleation and numerous cases were diagnosed by radical resection of lesions due to relapse and aggravation after conservative treatment^{13,14}. These prudent studies and our report demonstrate cases with long medical history, persistent inflammation, huge mass, recent aggressive behavior, including numbness and lymph node enlargement. Several recurrences and continuous uncomfortableness are commonly observed in cases with delayed diagnosis. Although these symptoms are nonspecific, clinicians should be aware of the malignant transformation of OD and synthetically judge of patients' history, clinical behavior, and CT/MRI image results. For cases without these characteristics, enucleation seems to be the safe way to exclude early stage PIOSCC.

Special thanks to you for your good comments.

Other changes:

1. language polishing is reperformed by Essaystar Group.
2. Recent references are added.
3. the contained figures are rearranged by PowerPoint.

We tried our best to improve the manuscript and made some changes in the manuscript.

These changes will not influence the content and framework of the paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.