

Peer Review File

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Reviewer A

Comment 1: An interesting case raising some important issues. I feel that the paper would benefit greatly from the case description being more concisely presented. The histological diagnosis and radiological technique needs more description. Major English language improvements required. With these improvements, I feel the paper could be accepted.

Reply 1: We are very sorry that some specifics about histological diagnosis and radiological technique were not described well. This was also pointed out by another reviewer. That has been rectified by adding detailed description in the main text and figure legends.

Changes in the text: “Somatostatin receptor 2A (SSTR2A) is expressed in phosphaturic mesenchymal tumors (PMT) and has been reported to be closely associated with TPIO. ⁶⁸Ga-DOTATATE is a somatostatin analog imaging agent and is widely used in PET/CT to identify the location of TIO lesions. A meta-analysis suggested that the imaging modalities based on somatostatin receptors outperformed F-FDG PET/CT in the detection of TIO, with Ga-DOTA-SST PET/CT performing slightly better than octreoscan-SPECT/CT.” were added to Line 175 to 181.

“Spindle cell proliferation and pathological characteristics of anaplastic hemangiopericytomas were observed on Hematoxylin & Eosin (H&E) staining of the neoplasm, while exact calcium salt deposition was not sought in the H&E-stained section. Immunohistochemical staining showed that CD56 was positive and CD31, CD34, ETS-related gene (ERG), and Syn were positive, while the percentage of KI67-positive cells was 1-2%.” were added to Line 193 to 199.

“PET/CT imaging showed that there was a high ⁶⁸Ga-DOTATATE uptake lesion in the left nasal cavity, indicating the neoplasm in the left nasal cavity was the potential lesion of osteomalacia.” and “Spindle cell proliferation and pathologic features of anaplastic hemangiopericytomas were observed in H&E staining of the neoplasm.” were added to Line 381 to 383 and Line 387 to 388 as legends of Figure 2 and 3.

Moreover, we added the imaging of Pelvic X-ray as Figure 1 to illustrate the bone disorder of patient intuitively and clearly.

Reviewer B

Comment 1: 1. Was serum FGF23 investigated in the blood test?

Reply 1: We are sorry that the serum FGF23 of the patient was not detected due to that it is not a conventional testing item in the hospital. It is a defect of this case report that there was a lack of the comparison of serum FGF23 levels before and after surgery. We have expounded that in the Discussion section of main text.

Changes in the text: “First, the serum FGF23 levels were not measured before and after surgery.” was added to Line 292 to 293.

Comment 2: Did the tumor in figure 2 stain with hematoxylin and eosin?

Reply 2: Yes, the figure 2 illustrates the H&E staining of tumor tissue. We are sorry that it was not explained clearly in both the main text and figure legends. We have added the corresponding explanation both in main text and figure legends.

Changes in the text: “Spindle cell proliferation and pathological characteristics of anaplastic hemangiopericytomas were observed on Hematoxylin & Eosin (H&E) staining of the neoplasm, while exact calcium salt deposition was not sought in the H&E-stained section. Immunohistochemical staining showed that CD56 was positive and CD31, CD34, ETS-related gene (ERG), and Syn were positive, while the percentage of KI67-positive cells was 1-2%.” were added to Line 193 to 199.

“Spindle cell proliferation and pathologic features of anaplastic hemangiopericytomas were observed in H&E staining of the neoplasm.” was added to Line 387 to 388 as legends of Figure 2 and 3.

Comment 3: Did the tumor stain on immunohistochemistry such as FGF23 or somatostatin receptor 2?

Reply 3: The FGF23 or somatostatin receptor 2 levels was not detected in the tumor tissues by immunohistochemistry (IHC). This is another defect of this case report. However, increasing uptake of ⁶⁸Ga-DOTATATE, a somatostatin analogs imaging agent, was illustrated by ⁶⁸Ga-DOTATATE PET-CT imaging, which suggested that the tumor tissue highly expressed somatostatin receptor (SSTR). Although that could not replace the directly detection method of SSTR (e.g. IHC staining), it suggested indirectly the high levels of SSTR in tumor tissues. It was also expounded in the Discussion section.

Changes in the text: “Second, FGF23 or somatostatin receptor (SSTR) was not detected in tumor tissues, although the PET/CT result could demonstrate the high expression of SSTR in tumor tissues.” was added to Line 293 to 295.

Comment 4: I suggest the addition of X-ray radiography or MR figures to understand bone condition visually.

Reply 4: That’s a pretty suggestion. We have added a result as figure 1 (previous figure 1 and 2 was then postponed as figure 2 and 3). The bone ECT result can be clearly illustrate the abnormal general bone structure caused by paraneoplastic syndrome.

Changes in the text: Imaging of pelvic radiograph was added as Figure 1, and its figure legends is “Figure 1: Pelvic X-ray of the patient indicating the abnormalities in bone. X-ray result showed the patient has degeneration of pelvis and bilateral hip. Osteosclerosis could be found under the ilium surface of bilateral sacroiliac joints. Moreover, the joint space was obscured.”.

Comment 5: Phosphaturic mesenchymal tumor arising in the head and neck is extremely rare, so I suggest the addition of literature cases treated with surgery.

Reply 5: It is also a nice advice. However, according to the policy of editorial office the words and reference paper of case report were limited to be no more than 2500 and 20 respectively, which severely restricts the space of discussion on that. So that it is difficult to comprehensively review previously published literature cases of phosphaturic mesenchymal tumor treated with surgery. All the same, the rare and multiple clinical characteristics of phosphaturic mesenchymal tumor was mentioned and discussed in the Discussion section as much as possible by citing several related cases and review papers.

Changes in the text: “Connections between TIO and phosphaturic mesenchymal tumor (PMT) were established in the 1950s. PMT is the main cause of TIO, although not the only one. About 80% of cases of TIO are due to PMT, and another 20% share other types of mesenchymal tumors, including hemangiopericytoma (HPC), giant cell tumor of bone (GCTB), and osteosarcoma. PMT presenting in the head and neck region is also relatively rare. According to a case review, there were only 71 cases of head and neck PMT published during 1972 to 2015. In adult patients, there are more female patients with PMT of the head and neck than males according to the case review. Understanding the focal sites of tumors would have supported a diagnosis of PMT and TIO, PMT in the head and neck prefers to appear at extraoral sites instead of intraoral sites. The paranasal sinuses and mandibles are the two most common sites of PMT of the head and neck according to the literature review. Most head and neck PMT cases are benign. However, a small number of head and neck PMT cases will recur and metastases are observed in very few cases, which is related to the prognosis of patients and deserves the attention of clinicians. Typical histological features of PMT can be summarized as bland spindle cells with vascularity and numerous multinucleated giant cells embedded in a chondromyxoid matrix with focal areas of calcification. However, depending on histological features alone they are not suitable for diagnosis due to a lack of specificity. Moreover, FGF23 serum or tumor testing by detecting FGF23 protein or mRNA expression, as well as PET/CT are beneficial for PMT and TIO diagnosis.

Overall, elucidation of the clinical characteristics, anatomical location and histological characteristics of head and neck PMT and its induced TIO are pending further investigation due to its very low incidence rate. Reviewing past published cases is a commonly used approach to understand the clinical features of the diseases, especially when the incidence of the disease incidence is low. However, the results of the literature review may not be accurate due to multiple potential biases. To fully and accurately investigate PMT, retrospective epidemiological studies that target an entire district and adequate exploring clinical studies should be considered in the future.” was added to Line 234 to 263.

Reviewer C

Comment 1: The outline of the case is appropriate as presented, however, the readability of the document needs major improvement. I would suggest using past tense for the case rather than present tense.

Reply 1: We are so sorry that there are lots of grammatic issues in the manuscript, which may severely impair the readability. Therefore, the manuscript has been polished by

commercial company. We hope it could improve the language quality of the revised manuscript.

Changes in the text: There are a large number of trivial changes about grammatic issues in the manuscript. It is not suitable to list all changes here. However, all changes about grammatic issues and non-grammatic issues could be found in the revised manuscript via track mode of Microsoft Word.