Editor-in-Chief, World Journal of Clinical Cases

Dear Editor:

We have resubmitted our revised manuscript, **"Spinal giant cell-rich osteosarcoma-diagnostic dilemma and treatment strategy: case report"**. We are grateful for this opportunity to revise and thank you and all the reviewers very much for your time, effort, and helpful comments. We have completed all the requested revisions, and now hope that you will find our work qualified for publication.

We look forward to your reply. Thank you very much.

Sincerely,

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Reviewer 1

Comment 1: GCRO is a rare variant of conventional osteosarcoma that is easily misdiagnosed as GCT, please describe the key and detailed points in differential diagnosis. What are the unique insights that this study presented? please give the description.

Authors' Response:

Thank you for your constructive comment. As suggested, we briefly reviewed the reported cases of GCRO. The differential diagnosis between GCT and GCRO can rely on radiographic features and pathology. We have revised this section in the Revised Text, Page 7, Line 137:

Radiographically, the radiographic feature of GCRO and GCT are similar in the literature. However, it was reported most GCRO had little periosteal reactions, while periosteal reaction was seen in 10-30% of GCTs. Besides, the periosteal reaction identified in GCTs usually presented in long bones and the spinal location of the present case may further hinder the identification of these radiographic findings (1). Histologically, both GCT and GCRO consist of diffuse infiltration of an abnormally increased number of giant cells (2). The abundant giant cells in GCROs could thereby almost swamp the sarcoma cells, making GCRO to be easily misdiagnosed as GCT in pathology (3). Moreover, the giant cells in GCRO and GCT both shared a common H3F3A mutation, an osteoclast-like activity, and a tendency to cause bone resorption (4). Therefore, radiolucency in X-ray images and osteolytic lesions in CT is the commonly shared radiographic feature between GCT and GCRO (2,4,5). The key diagnostic feature to distinguish CGRO from GCT is still the presence of eosinophilic and irregularly shaped osteoids, which are usually surrounded by a rim of osteoblasts. Furthermore, the key sarcomatous features of GCRO composed of atypical mononuclear oval to plump spindle cells with anaplasia and nuclear pleomorphism, invasive permeative infiltration, and formation of irregularly contoured eosinophilic osteoid, which are unlikely be present in GCT (2,4,6). Moreover, recent studies showed MDM2 and CDK4

are amplified in low-grade OS, which can potentially help distinguish GCT and GCRO. It was also reported that a high Ki67 proliferative index of over 20 % in GCRO which is found to be useful in its differentiation from GCT (6,7,8).

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Reviewer 2

Comment 1: The history and the examination part can be combined with relevant positive findings as a single paragraph to make it more seamless to readers.

Authors' Response:

Thank you for your valuable suggestions. As suggested, we combined the examination part with relevant positive findings as a single paragraph to make it more seamless to readers

Revised text:

(Page 5, Line 98)

History, physical examination, and image examinations.

The patient with unremarkable history complained of insidious onset of intermittent back pain followed by bilateral ascending paresthesia for 4 months. Neurological examination revealed paresthesia below T5 level, 5/5 muscle strength in all of her four limbs, and bilaterally normal reflexes. The spinal CT and magnetic resonance imaging (MRI) revealed a collapsed T2 vertebra with an enhancing osteolytic mass that extends into the epidural and paraspinal region (Figure 1, A-C). Bone scan showed an active bone lesion at the upper thoracic spine (Figure 1D).

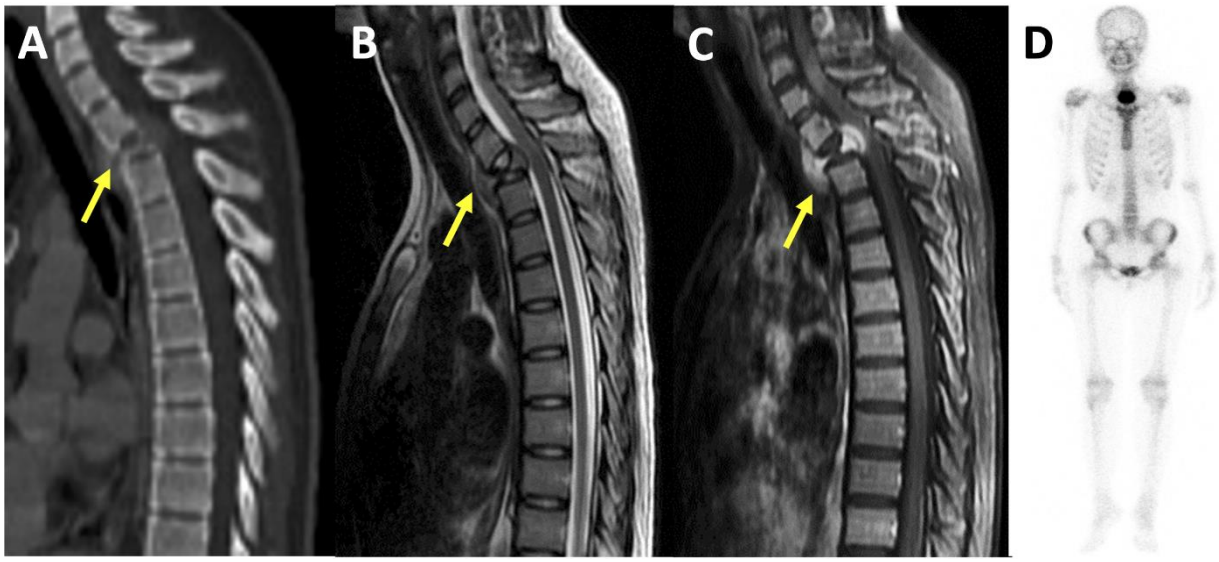

Figure 1. Preoperative radiographic evaluation

Preoperative computed tomography (A) demonstrating collapsed T2 vertebra (Arrow). Preoperative magnetic resonance imaging (B, C) revealed vertebral body mass with paraspinal and epidural paraspinal extension and gadolinium enhancement (C). Bone scan (D) showing an active bone lesion at the upper thoracic spine.

Comment 2: Minor language errors needs rectification.

Authors' Response: Thank you for your constructive comment. As suggested, we revised the language errors by a native English speaker to improve the clarity of our manuscript.

Comment 3: Although the case reported didn't encounter any recurrence, kindly mention the natural history of the disease and the follow-up guidelines

Authors' Response: Thank you for your valuable comments. In order to address these issues, we have incorporated two paragraphs in the discussion section.

Revised text: (Page 8, Line 172, regarding to the natural history of GCROs)

The survival rate of GCROs is similar to that of high-grade osteosarcoma (15) ranging from 60% to 70% at 5 years and decreases to approximately 20%–30% in patients with metastatic disease (5, 17), long-term local control is achievable with complete resection. The spinal location of the GCRO could impact its prognosis since complete resection with clear surgical margins is associated with better survival (9). Complete spinal GCRO resection could be more technically challenging or require more aggressive approaches given the proximity of the neural, vascular, and visceral structures to the spinal column compared to the long-bone counterparts (16). Therefore, the survival rate of primary osteosarcoma in pediatric spine is 18% at 5 years and 7% with distant metastasis. (21) However, grossly-total tumor resection should be attempted since it directly affects the prognosis (2,7,8). A recent meta-analysis study had also revealed beneficial outcome after salvage surgery for residual primary spinal osteosarcoma (22). In the present case, given the relationship between the extent of resection and prognosis, a second salvage operation following neoadjuvant chemotherapy was performed and grossly-total resection was achieved. The present case showed that long-term local control is achievable following complete resection of salvage surgery and adjuvant chemoradiation even in spinal GCRO with previous subtotal resection.

(Page 9, Line 189, regarding to the follow-up protocol)

With limited knowledge, we propose in addition to regular physical and neurological exams, a whole-body bone scan 6-month after salvage surgery is suggested to exclude any distant metastasis. A spinal CT is indicated to evaluation the degree of bony fusion on 3-6 months postoperatively. MRI scans every 6-month in the first 2 years and yearly in the subsequent years are mandatory to identify any recurrent tumor locally.

Science editor

Comment 1: This manuscript reported a case of giant cell-rich osteosarcoma (GCRO) of the spine at T2. This case is rare, and it is suggested that the history and examination sections could be combined as a paragraph with the relevant positive findings, complementing key and detailed points describing the differential diagnosis, as well as the new information presented by this study.

Authors' Response:

Thank you for your valuable suggestions, we have revised this section in the response to comment 1 by reviewer 2. As suggested, we combined the examination part with relevant positive findings as a single paragraph to make it more seamless to readers. Also, we illustrate the key points of the differential diagnosis between GCRO and GCT radiographically and histopathologically in our response to comment 1 by reviewer 1.

Company editor-in-chief

Comment 1: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Authors' Response: Thank you for your kind reminder. We have prepared the revised submission files as required.