Round 1

Dear Editor,

Here we submitted the revised Manuscript NO.: 84937, Case Report entitled “Posterior pedicle screw fixation combined with local steroid injections for treating axial eosinophilic granulomas and atlantoaxial dislocation in a 6-year-old boy”.

We thank you for your consideration of the manuscript for publication and thank the Reviewers for the insightful comments, which were not only scientifically meritorious but also extremely helpful in directing our efforts to enhance the scientific quality of this manuscript. We have attempted to address the Reviewers' concerns and a detailed point by point response is provided below. The revised parts are highlighted in Red

We believe that the revisions following the Reviewers' advice have substantially improved the manuscript and we hope that the revised manuscript is suitable for publication.

Thank you for your consideration.

Best regards,

Chengquan Tu and Zhida Chen, Bin Lin

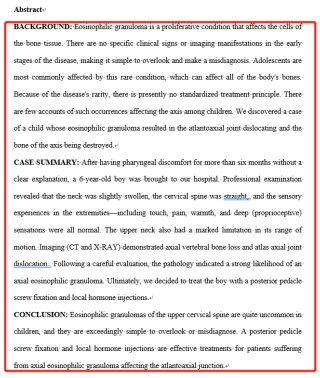
Reviewer #1:

1- Modifications must be made to the title of the paper so that it more accurately reflects the purpose for which the current study was conducted.

We have modified the title of the paper as requested, in order to better highlight the purpose of the research. We have modified the title from “Posterior pedicle screw fixation combined with local hormone injections in the treatment of axial eosinophilic granulomas in a 6-year-old boy” to “Posterior pedicle screw fixation combined with local steroid injections for treating axial eosinophilic granulomas and atlantoaxial dislocation in a 6-year-old boy”.

2- Shorten the abstract of the study to make it more attractive and easier.

We have trimmed the summary of the article by removing some lengthy sentences.

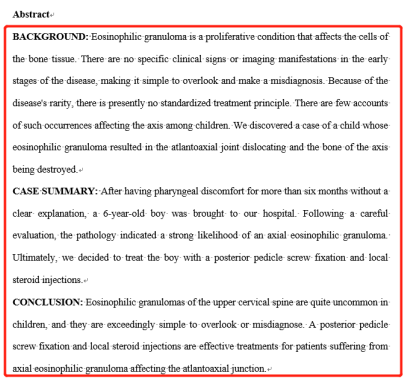


Abstract

BACKGROUND: Eosinophilic granuloma is a proliferative condition that affects the cells of the bone tissue. There are no specific clinical signs or imaging manifestations in the early stages of the disease, making it simple to overlook and make a misdiagnosis. Adolescents are most commonly affected by this rare condition, which can affect all of the body's bones. Because of the disease's rarity, there is presently no standardized treatment principle. There are few accounts of such occurrences affecting the axis among children. We discovered a case of a child whose eosinophilic granuloma resulted in the atlantoaxial joint dislocating and the bone of the axis being destroyed.

CASE SUMMARY: After having pharyngeal discomfort for more than six months without a clear explanation, a 6-year-old boy was brought to our hospital. Professional examination revealed that the neck was slightly swollen, the cervical spine was straight, and the sensory experiences in the extremities—including touch, pain, warmth, and deep (proprioceptive) sensations were all normal. The upper neck also had a marked limitation in its range of motion. Imaging (CT and X-RAY) demonstrated axial vertebral bone loss and atlas axial joint dislocation. Following a careful evaluation, the pathology indicated a strong likelihood of an axial eosinophilic granuloma. Ultimately, we decided to treat the boy with a posterior pedicle screw fixation and local hormone injections.

CONCLUSION: Eosinophilic granulomas of the upper cervical spine are quite uncommon in children, and they are exceedingly simple to overlook or misdiagnose. A posterior pedicle screw fixation and local hormone injections are effective treatments for patients suffering from axial eosinophilic granuloma affecting the atlantoaxial junction.



Abstract

BACKGROUND: Eosinophilic granuloma is a proliferative condition that affects the cells of the bone tissue. There are no specific clinical signs or imaging manifestations in the early stages of the disease, making it simple to overlook and make a misdiagnosis. Because of the disease's rarity, there is presently no standardized treatment principle. There are few accounts of such occurrences affecting the axis among children. We discovered a case of a child whose eosinophilic granuloma resulted in the atlantoaxial joint dislocating and the bone of the axis being destroyed.

CASE SUMMARY: After having pharyngeal discomfort for more than six months without a clear explanation, a 6-year-old boy was brought to our hospital. Following a careful evaluation, the pathology indicated a strong likelihood of an axial eosinophilic granuloma. Ultimately, we decided to treat the boy with a posterior pedicle screw fixation and local steroid injections.

CONCLUSION: Eosinophilic granulomas of the upper cervical spine are quite uncommon in children, and they are exceedingly simple to overlook or misdiagnose. A posterior pedicle screw fixation and local steroid injections are effective treatments for patients suffering from axial eosinophilic granuloma affecting the atlantoaxial junction.

3- The introduction to the study consists of a single paragraph, which needs to be split into three. The first paragraph should highlight the significance of the current study, the second paragraph should describe the knowledge gap that the current study seeks to fill, and the third paragraph should review the research problem and how to solve it within the context of the current study's objective.

We have revised the introduction into a three-part structure. In the first part, we highlighted the significance of the current research. In the second part, we described the knowledge gaps in the

current research. In the third part, we explained how we treated the disease.

INTRODUCTION

Eosinophilic granulomas (EGs) are osteolytic tumor-like masses that usually develop slowly without presenting with any clinical symptoms when they are in their early stages [1, 2]. Most lesions of EG are isolated, and they can affect the whole skeletal system [1, 3]. Numerous Langerhans cells are proliferating, and eosinophils and lymphocytes are invading the diseased tissue. Bone EG has a modest occurrence, at about 1/1500000 [1, 4]. With a male to female ratio of roughly 2 to 5:1 and a spine prevalence of 6.5% to 25%, the majority of cases affect children between the ages of 5 and 14 [4-6].

According to previous reports, cervical EG is a rare disease among children [1, 3]. There isn't yet a standard treatment philosophy, therefore each patient requires an individual plan of care that is tailored to their specific needs.

A boy with axial EG with dislocation of the atlantoaxial joint was treated by posterior pedicle screw fixation combined with local steroid injections at the hospital's Spine Surgery department.

4- Add recent references to the CASE PRESENTATION section that support the methods used by the researchers in the following paragraphs: Physical examination, Laboratory examinations, Imaging examinations, and Surgical methods.

In response to this revision suggestion, we have incorporated the normal values of our own hospital laboratory's testing indicators and cited an article on the surgical methods for treating the disease.

Laboratory examinations

According to laboratory testing, the regular blood and procalcitonin levels were normal. The hypersensitive C-reactive protein (CRP) level was 21.78 mg/L, and the erythrocyte sedimentation rate (ESR) was 78 mm/h.

Laboratory examinations

According to laboratory testing, the regular blood and procalcitonin levels were normal. The hypersensitive C-reactive protein (CRP) level was 21.78 mg/L (Normal CRP values for adults and children are 0.068-8.2 mg/L.), and the erythrocyte sedimentation rate (ESR) was 78 mm/h (Normal ESR values are 0 mm/h to 15 mm/h for men and 0 mm/h to 20 mm/h for women.).

TREATMENT

The patient was admitted to complete the relevant examinations and was performed biopsy to clarify the cause. Figure 5 shows the hyperextended position in which cranial traction reduction was carried out. Regular bedside X-rays were taken to assess the decrease in atlantoaxial joint dislocation following traction, and the traction line and weight were promptly adjusted. We employed pedicle screws to regain spinal stability while simultaneously administering local corticosteroid injections to treat the eosinophilic granuloma intraoperatively.

TREATMENT

The patient was admitted to complete the relevant examinations and was performed biopsy to clarify the cause. Figure 5 shows the hyperextended position in which cranial traction reduction was carried out. Regular bedside X-rays were taken to assess the decrease in atlantoaxial joint dislocation following traction, and the traction line and weight were promptly adjusted. According to the categorization of atlantoaxial joint dislocation given by Wang et al [4], the child had Type II (Reducible dislocation), atlantoaxial instability, and required surgical therapy. We employed pedicle screws to regain spinal stability while simultaneously administering local corticosteroid injections to treat the eosinophilic granuloma intraoperatively.

4 **Wang S**, Wang C, Yan M, Zhou H, Dang G. Novel surgical classification and treatment strategy for atlantoaxial dislocations. *Spine (Phila Pa 1976)* 2013; **38**(21): E1348-1356 [PMID: 23823573 DOI: 10.1097/BRS.0b013e3182a1e5e4]

5- In the final paragraph of the discussion section, the strengths and limitations of the current study and the future directions of the current study should be described.

In the last paragraph of the discussion section, we added the advantages and limitations of the study as well as the future development directions for this research.

CONCLUSION

Axial eosinophilic granuloma with dislocation of the atlantoaxial joint in children can be effectively and safely treated with posterior pedicle screw fixation and local hormone injections. This course of therapy can not only relieve spinal cord compression, acquire dependable fixation, and restore the stability of the spine, but it can also lessen localized edema and effectively manage pain. Clinically, this course of therapy may be beneficial for children with axial eosinophilic granuloma complicated by atlantoaxial joint dislocation.

computed tomography (CT) alone is not appropriate.

In general, our research has made a significant contribution to the use of this treatment method for related diseases. Our study has found significant therapeutic effects of this treatment, indicating broad potential applications. However, we must acknowledge limitations of this study, primarily reflected in the small sample size. Future research should build upon our findings and continue to collect more cases to further establish the therapeutic efficacy of this treatment and explore optimization methods.

CONCLUSION

6- I don't think it is necessary to include these subheadings (Clinical characteristics, Treatment strategy) in the discussion section, so I encourage authors to keep the paragraphs while eliminating the subheadings.

We have removed the subheadings in the discussion section, including Clinical characteristics and Treatment strategy.

7- Rewrite the study's conclusion to elucidate whether the research problem was resolved; in other words, did the current study accomplish its objective? This issue should be addressed within the study's conclusion.

In accordance with the reviewers' comments, we have rewritten the conclusion, highlighting the effective treatment of the boy's disease and the satisfactory resolution of clinical issues.

CONCLUSION

Axial eosinophilic granuloma with dislocation of the atlantoaxial joint in children can be effectively and safely treated with posterior pedicle screw fixation and local hormone injections. This course of therapy can not only relieve spinal cord compression, acquire dependable fixation, and restore the stability of the spine, but it can also lessen localized edema and effectively manage pain. Clinically, this course of therapy may be beneficial for children with axial eosinophilic granuloma complicated by atlantoaxial joint dislocation.

CONCLUSION

After surgery, the spinal cord compression in the patient was relieved, the stability of the spine was restored, local edema reduced, and the pain significantly eased. The patient has returned to a normal life at present. Axial eosinophilic granuloma with dislocation of the atlantoaxial joint in children can be effectively and safely treated with posterior pedicle screw fixation and local steroid injections. Clinically, this course of therapy may be beneficial for children with axial eosinophilic granuloma complicated by atlantoaxial joint dislocation.

8- Some references are old and require revision. I recommend using references from within the past five years.

Regarding this point, due to the low incidence rate of this disease and the lack of standardized treatment methods, some relevant literature may be relatively outdated. We have tried our best to select the most up-to-date references. We hope for your understanding.

Reviewer #2:

The authors present a case report of clinical interest, which is illustrated by interesting images and follow up. The subject falls within the scope of the journal. Description and discussion of the findings are well done and well-founded. The bibliography is pertinent and current, however can be expanded (see attached file). The text needs improvement, and the wording should be comprehensively reviewed. Excerpts that deserve special attention were marked in yellow in the attached fille.

We have made modifications to the language and wording as per the reviewers' suggestions, and added relevant literature as suggested by the reviewers.

the most common manifestation of the disease, while extraosseous involvement was less frequent. INCLUDE:

Schmidt S, Eich G, Geoffray A, et al. Extraosseous Langerhans Cell Histiocytosis in Children. Radiographics. 2008;28(3):707-26.

Classification of Histiocytic Disorders in Children following:

Histiocytosis syndromes in children. Writing Group of the Histiocyte Society. Lancet 1987;1:208–209.

8 **Jiang L**, Liu ZJ, Liu XG, Zhong WQ, Ma QJ, Wei F, Dang GT, Yuan HS. Langerhans cell histiocytosis of the cervical spine: a single Chinese institution experience with thirty cases. *Spine (Phila Pa 1976)* 2010; **35**(1): E8-15 [PMID: 20042947 DOI: 10.1097/BRS.0b013e3181b8aa2d]

9 **Schmidt S**, Eich G, Geoffray A, Hanquinet S, Waibel P, Wolf R, Letovanec I, Alamo-Maestre L, Gudinchet F. Extraosseous langerhans cell histiocytosis in children. Radiographics. 2008 May-Jun;28(3):707-726; [PMID: 18480480 DOI: 10.1148/rg.28307510]

10 Histiocytosis syndromes in children. Writing Group of the Histiocyte Society. Lancet. 1987 Jan 24;1(8526):208-209. [PMID: 2880029]

11 **Prasad GL**, Divya S. Eosinophilic Granuloma of the Cervical Spine in Adults: A Review. *World Neurosurg* 2019; **125**: 301-311 [PMID: 30771538 DOI: 10.1016/j.wneu.2019.01.230]

12 **Feng F**, Tang H, Chen H, Jia P, Bao L, Li JJ. Percutaneous vertebroplasty for Langerhans cell histiocytosis of the lumbar spine in an adult: Case report and

Langerhans cells is observed with a lobulated nucleus of thin chromatin and moderately abundant eosinophilic cytoplasm with some nuclear atypias and variable mytotic activity. On the other hand, immuno-histochemical study reveals the presence of Birbeck granules, positivity for S-100 and CD1a (representing diagnostic certainty). Include:

Langerhans cell histiocytosis in a 3-year-old girl: a case report and literature review. Pol J Pathol. 2009;60:134–7.

Grois N, Tsunematsu Y, Barkovich AJ, et al. Central nervous system disease in Langerhans cell histiocytosis. Br J Cancer Suppl. 1994;23:S24–S28.

Iyeyasu JN, Vaz ACM, Reis F, Altemani J, Queiroz LS, Carvalho KM. Langerhans cell histiocytosis diagnosed in an elderly patient. Radiol Bras. 2012 Jul/Ago;45(4):241–243.

The main clinical manifestation of this 6-year-old male child was neck pain and obvious

Fig.2 (a– d) Atlantoaxial subluxation and bone destruction at the top edge of the axial vertebral body are preoperative CT findings.

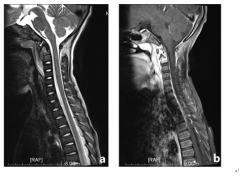


Fig.3 (a-b) The lesions were noticeably enhanced in the preoperative MRI, which showed long T1 and long T2 signals on the axis, striated long T1 and long T2 signals in the retropharyngeal and prevertebral spaces, and long T1 and long T2 signals in these regions.

You should describe that this T1 is after contrast, and description should be modificated

13. **Duda-Szymańska J**, Wierzchniewska-Ławska A. Langerhans cell histiocytosis in a 3-year-old girl: a case report and literature review. Pol J Pathol. 2009;60(3):134-137. [PMID: 20069507]
14. **Grois N**, Tsunematsu Y, Barkovich AJ, et al. Central nervous system disease in Langerhans cell histiocytosis. Br J Cancer Suppl. 1994;23:S24–S28. [PMID: 8075002; PMCID: PMC2149701]
15. **Iyeyasu JN**, Vaz ACM, Reis F, Altemani J, Queiroz LS, Carvalho KM. Langerhans cell histiocytosis diagnosed in an elderly patient. Radiol Bras. 2012 Jul/Ago;45(4):241–243. [PMID: 22870452 · DOI: 10.1590/S0100-39842012000400016]

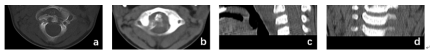


Fig.2 (a– d) Atlantoaxial subluxation and bone destruction at the top edge of the axial vertebral body are preoperative CT findings.

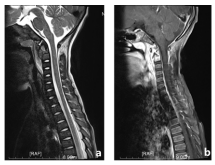


Fig.3 (a-b) Cervical spine MRI with contrast enhancement revealed odontoid destruction and abnormal signals in the retropharyngeal and prevertebral spaces.

Round 2

Reviewer#1: the archive Answering Reviewers was identical to Manuscript file. The authors made a mistake.

Answer: We apologize for an inconvenience caused. We have provided the correct "Answering Reviewers".

Reviewer#2: Dear Authors, The method you used to amend the paper is unclear, making it difficult for my task as an arbitrator to determine whether the required amendments were made or not, as I expected to find a clear and logical response to each of the amendments I requested separately (point by point response), or at the very least to change the font color of the places where the modifications were added in the revised version of the article. All of this is missing from the manuscript, and I cannot accept it unless the author(s) accomplish what is necessary in a transparent manner. //Good Luck//

Answers: We apologize for an inconvenience caused. We have provided the correct "Answering Reviewers". The revised parts are highlighted in Red We believe that the revisions following the Reviewers' advice have substantially improved the manuscript and we hope that the revised manuscript is suitable for publication. Thank you for your consideration.