Author's response to reviews

Title: Chronic multifocal non-bacterial osteomyelitis in hypophosphatasia mimicking malignancy

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Author's response to reviews:

Dear Lolu da-Silva, assistant editor, BMC series

We would like to answer the reviewers' questions in detail regarding the manuscript with the title Chronic multifocal non-bacterial osteomyelitis in childhood hypophosphatasia mimicking malignancy sent to BMC pediatrics for publication.

Reviewer Prof. A.G. Jurik stated at first that in the second patient multifocality of the inflammatory lesion has not been proven, since the spinal lesions were not biopsied. We agree that multifocality is not finally proven in this case. However, we have to state that biopsy of spinal lesions are difficult to perform technically, especially when the vertebrae are compressed. Since biopsy was solely done for diagnostic reasons, it seemed appropriate and sufficient to biopsy the rib lesion only. Since histology did not reveal signs of trauma in the rib lesion, but classical sterile lympho-plasmocytoid osteomyelitis, it seemed probable that the spinal lesions were also of inflammatory nature. This consideration is supported by the oedematous changes of the 8th vertebral body (MRI, figure 2e), which are located at its posterior part without signs of compression. Mechanical lesions probably would have involved the anterior part of this vertebra. In addition, the fact that the 10th vertebra is not involved makes the distribution of the lesions look scattered and not of typical traumatic origin. We have included the second patient in the abstract summary.

We have deleted the statement Growth hormone.." from the introduction and shifted it to the discussion, as suggested by both reviewers.

We have deleted the abbreviation ENT.

We have explained why we know that the mutation was of maternal origin: it was found in the mother's genome.

The rib lesion was also analysed by MRI of the thorax. It did show a strong T2/TIRM/STIR signal, which was completely resolved 12 months later. We have added this information to the case description.

Please see our comment above related to suspected multifocality in case 2.

Levels of Ca and phosphorus were normal in both patients, comparable to a group of childhood hypophosphatasia patients reported previously by us. We have not focused on the biochemical description of the data in this report, because we wanted to focus on the MRI changes etc..

We have added a more detailed section in the discussion dealing with the hypophosphatasia associated changes in the bone structure, which can resemble vitamin D resistant rickets or osteomalacia clinically and on x-rays. We have discussed the role of bone fractures and osteomalacia in relation to inflammatory changes seen in histology, as suggested by the reviewer.

We have added, as suggested, a discussion on structurally altered rib cage like pigeon-chest in hypophosphatasia and its relation to repetitive trauma at the costochondral junction.

Findings in diagnostic imaging in the two patients were not different in extent and structure from a cohort of patients with chronic osteomyelitis (CNO, CRMO) in whom hypophosphatasia had been excluded. This
information was added to the discussion, as suggested.

References were updated in the text in this regard.

Reviewer Prof. H. Orimo suggested to restructure the abstract and discussion and to introduce a conclusion. We have followed his suggestions.

We have added an explanatory section to the description of case 2, as suggested by the reviewer: We suggested that a partial defect in the TNSALP gene was present. She may be a carrier of one severely mutated allele of alkaline phosphatase, because slight elevation of plasma pyridoxal levels has been demonstrated in obligatory heterozygotes (parents of index patients) with severe alleles [8]. In addition, we have corrected the wording regarding the carrier status of this patient throughout the manuscript.

I have added sections on competing interests, authors' contributions and acknowledgements to the end of the manuscript.

We have added a section on the probability of hypophosphatasia diagnosis at the end of the second case description. We completely agree with the reviewer that this patient does seem to be a heterozygous carrier of the hypophosphatasia trait. We already had mentioned this in the paper before. Now we have extended this aspect, as suggested.

We have expanded the Background section of the abstract in order to give a better introduction on HP, as suggested.

We have partly shifted the last 4 lines of the introduction to the discussion section, as suggested. We have chosen not to expand the Introduction section, since we have revised the abstract summary and the conclusion in detail instead.

Unfortunately we have not measured prostaglandin concentrations in these 2 patients.

We hope that with this major revision we have met the criteria of both reviewers. We are very thankful for their comments.

Sincerely yours
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