Reviewer’s report

Title: A case of Molecularly Profiled Extraneural Medulloblastoma Metastases in a Child

Version: 1 Date: 09 Aug 2017

Reviewer: Maria A. Lastowska

Reviewer's report:

The paper presents a case report describing extraneural metastases in a child with medulloblastoma. Since this is a rare clinical manifestation of the disease, molecular characteristic of tumour warrants particular attention.

The reviewer has the following concerns with the manuscript:

1) It is unclear what was the basis for diagnosis of original tumour since no histopathological examination results were presented in the case presentation section.

Diagnosis of 'medulloblastoma with classic morphology' and immunohistochemistry results refer to mandibular sample only, is it right?

2) Molecular investigation of metastatic tumour included next generation targeted exome sequencing.

In view of the reviewer, the results do not allow for classification of tumour into one out of four established groups of medulloblastoma. The plot in Figure 4 does not support the presented in the text results concerning monosomies, with exception of chromosome 3. Amplification of ETV1 and SOX9 is not indicated on the plot. Therefore, the suggestion by the authors that tumour belongs to group 4 is at least speculative.

Also, from the methodological point several questions arise:

a) It is not clear what genes were included into oncopanel used in the study. Please provide the link to the list of analyzed genes and information what was the criteria for their selection.

b) In molecular profiling of tumours the "gold standard" is to use matched patient's germline DNA to establish which abnormalities detected in tumours samples are somatic and are relevant to the oncogenic processes. Did the authors taken into account the patient's germlinal material for the identification of somatic mutation?
c) Taken into consideration that The Association for Molecular Pathology and College of American Pathologists recommend a minimal depth of coverage>250 reads per tested amplicon or target for somatic variant detection (http://dx.doi.org/10.1016/j.jmoldx.2017.01.011), obtained in the study NGS data carry increased risk of possibility of false-positive or false-negative results.

Please specify what was the pipeline of NGS data analysis. Supplementing this information is particularly important as the author's pointed that 'No notable somatic mutation were detected'.

Therefore, the absence of mutation in tumour sample may be somehow surprising. Do the authors have hypothesis explaining these results?

Summarising this point, the reviewer strongly suggests an introduction of additional relevant method (e.g. methylation profiling) for identification of established molecular type of medulloblastoma in the presented case. As it stands, the title of this paper is overstated, bearing in mind obtained molecular results. The authors themselves underline in the discussion an importance of molecular group detection and this is not supported by presented here outcome of investigation.

3) Molecular analysis revealed amplification of MYCN, but in the abstract and in the description to Figure 4 MYC amplification is presented. Please clarify this discrepancy.

4) References cited throughout the text do not correspond to the numbers in the list of references.

5) A statement that "group 3 and group 4 tumours recur almost exclusively with extraneural metastases"... is not true, since metastases occur also within central nervous system.

A few minor comments are:

- Figure 2A is very distorted, also introduction of the arrows showing described features would be helpful for the readers.

- The name of gene should be written in italics.

- Irregularities in writing of Medulloblastoma or medulloblastoma

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No
Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?  
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?  
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English  
Please indicate the quality of language in the manuscript:

Acceptable

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