Reviewer’s report

Title: DNA Methylation Alterations in Grade II- and Anaplastic Pleomorphic Xanthoastrocytoma

Version: 3
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Reviewer: Gianluca Marucci

Reviewer’s report:

The Authors have analyzed the DNA methylation profiles of PXA. This is a well-written, potentially interesting paper, which details previous literature in a comprehensive manner. However I have some reservations about this manuscript.

Major Compulsory Revisions

1. Frequently in the paper PXA is defined as a benign tumor! PXA is not a grade I tumor (like pilocytic astrocytoma) and correctly the Authors assert that it shows a 10-years survival rate of 70%. Thus it is more appropriate to define it as a low grade glioma.

2. Page 6, the Authors state “tissue obtained from epilepsy neurosurgical procedures was included in the study as normal control”: it is known that DNA methylation changes are observed in epileptic specimens [Kobow K, El-Osta A, Blümcke I. The methylation hypothesis of pharmacoresistance in epilepsy. Epilepsia. 2013 May;54 Suppl 2:41-7. / Kobow K, Blümcke I. The emerging role of DNA methylation in epileptogenesis. Epilepsia. 2012 Dec;53 Suppl 9:11-20]. Thus different control samples could be more useful.

3. Page 11, the Authors state “All PXA patients presented with a 4-8-week history of epileptic seizures”: PXAs are tumors included in the group of so called LEATs (long-term epilepsy associated tumors), i.e. tumors observed in patients who have been investigated and treated for drug-resistant seizure episodes for 2 years or longer. Thus the Authors should provide some considerations to explain the unusual short history of seizures observed in this PXA series.

4. Table 1. PXA 2 should be removed from the list of studied cases. As the Authors state “no tumor tissue was available for characterization”, thus its presence in this series does not make sense.

5. Table 1, PXA 6. More details should be provided about anaplastic features: which was mitotic index? What about necrosis?

6. Table 1 & Figure 1, PXA 4&5. This recurrent case, arisen in the oldest patient of the series (59y), represents the key case, determining a significant part of results. At page 4 the Authors assert that in PXA “MIB-1 labeling index is frequently <1%”; but in Figure 1 legend they state that MIB-1 was 10% in the
grade II PXA no. 4. In my opinion a MIB-1 value of 10% is too high for a grade II tumor; a tumor frequently defined in this manuscript by the Authors as benign. Thus the Authors should provide strong evidences that case no. 4 was not a malignant glioma ab initio: if this was true, it would explain the overlapping with DNA methylation alterations found in GBM and thus it would impair the meaning of the study.

7. Table 1. At page 17 the Authors assert “high frequency of BRAF V600E mutations in WHO grade II PXAs and PXAs with anaplastic features (65 and 66% of cases, respectively)”. This statement is completely correct and these percentages have been confirmed by other studies (for example Chappé C et al, Brain Pathol. 2013). However in the present PXA series only 1 out of 10 cases (10%!) presented BRAF V600E mutation. This huge difference in comparison to what usually observed should be explained by the Authors; otherwise it could be hypothesized that in this series have been included cases which are not PXA.

Minor Essential Revisions

1. In the abstract the number of studied PXA should be added.

2. The location of tumors should be added (how many were temporal cases?).

3. Page 17, line 1: the first ref. is wrong and must be replaced with [41].

4. Page 18 “This precocious intervention would probably revert on a better prognosis and increased life expectancy”: the statement is completely speculative and should be removed.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.