Reviewer’s report

Title: Ruptured hepatic metastases of cutaneous melanoma during treatment with vemurafenib: an autopsy case report

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Reviewer: Ryan Sullivan

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This is a well written description of a case of an unfortunate 44 year old woman with metastatic melanoma who died of a ruptured hepatic metastasis. While this is a case with a few important features that may are important to become part of the medical literature, there are a few major issues currently with the manuscript that must be addressed.

Major Compulsory Remarks:

1. Given the rapid growth of the patients hepatic metastasis in the setting of only 2 months of vemurafenib therapy, it is important to describe the type of BRAF analysis assay that was used and explain why the primary tumor was assayed instead of a metastatic lesion. There is expanding data that primary melanomas may be heterogeneous with respect to BRAF/NRAS mutational status, thus analysis of the primary tumors should be avoided as a general rule since the results may not reflect the BRAF/NRAS status of the metastatic clone. One exception to this would be a thick melanoma (especially a nodular melanoma), since the expanding clone(s) likely reflect those which will metastasize and thus would be expected to share the same BRAF mutational status. While the likeliest scenario in this case is that the patient had either primary refractory clones in the hepatic metastasis that ultimately grew and ruptured, it is important to better explain the BRAF testing methodology.

2. It is critical to know whether the patient had widespread growth of metastatic disease in the setting of vemurafenib or disease control everywhere but the metastatic lesion in the liver. Please provide a more comprehensive description of what was happening to her disease otherwise. For example, where the brain mets or lung mets larger, was it just one liver met or multiple that where expanding, was the disease found at autopsy in the kidneys, adrenal gland, and lymph nodes growing on imaging (or even seen on imaging).

3. When describing vemurafenib, it would be better to use primary data (Flaherty et al. NEJM 2010 - phase I trial, or Chapman et al. NEJM 2011 - phase III trial) instead of a review article. Along these lines, the mechanism of resistance data should also be primary data. There are two very comprehensive papers (Shi et al. Cancer Discovery 2014; 4:80-93; Van Allen et al. Cancer Discovery 2014; 4:94-109) that describe the various mechanisms of BRAF inhibitor therapy resistance on numerous samples. These should be used in place of the review
article from Swiaka et al. Also, vemurafenib is a selective inhibitor of the mutant 
BRAF protein or gene product, not the mutant BRAF gene. This should be 
changed (first sentence, second paragraph of the conclusions section).

4. The IHC is underwhelming and does not help determine what happened. 
Again, the primary tumor from 2008 may not be the best source of comparison to 
an autopsy specimen from Dec 2012 / Jan 2013. Since the ERK staining from the 
primary tumor and the hepatic tumor is sparse, it is impossible to make any 
conclusions about the effects of vemurafenib. It is interesting that there appears 
to be a difference in the ERK staining from the hepatic and lymph node met, but 
there is no context about the lymph node. Was this from the right inguinal surgery 
in 2008? from the autopsy? This must be clarified. In truth, performing more 
expanded exome sequencing on this patient would be the best way to try and 
figure out what happened. The mechanism of resistance, even the pathway that 
is unregulated at time of resistance is not clear, since it appears that both the 
MAPK and PI3K/AKT pathway is not unregulated in the hepatic met. This last 
aspect is very important, because mechanisms of resistance that bypass MAPK 
or PI3K pathway (re)activation are not well described.

Level of interest: An article of limited interest

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.