Author’s response to reviews

Title: Acute Hepatic Failure and Multi-System Organ Failure Secondary to Replacement of the Liver with Metastatic Melanoma

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Author’s response to reviews:

Reviewer #1:

1. Please justify the usage of the term TLS in this situation and how could you differentiate it from the terminal biochemical abnormalities which occur in every advanced disease as terminal event?

RESPONSE: We agree with the reviewers' concern that the clinical entity of 'tumor lysis syndrome' cannot be definitively proven in our case. The biochemical abnormalities seen in our case could potentially be explained by multi-system organ failure. The paper has been revised throughout to remove the comment/conclusion that 'tumor lysis syndrome' resulted in the clinical manifestations of the case.

2. The case report is sketchy and does not provide adequate information especially regarding adequate evaluation of the case prior to surgery. Clarify on the metastatic evaluation done at that time. Was liver evaluated with biochemical tests? CT scan or ultrasound? From further follow up of the case, it is unlikely that such large metastases would have appeared in 3 weeks time. They must have been existent at the time of surgery. If done, pre-surgical CT scan / ultrasound figures are desirable. If metastasis was present, what was the indication and purpose of surgery? If metastasis was absent, did 80% of liver get replaced by tumor in 3 weeks? Was metastasis detected elsewhere at second admission? Was the nodes N0 or N+ at presentation? How were they managed? A more detailed description of the case is desirable.

RESPONSE: The patient's melanoma was resected under local anesthestic. Following the surgery arrangements had been made to image the patient's abdomen, however this had not been completed within the 3 weeks of the surgery and the patient's presentation to hospital. Biochemical assessment was first reported at time of presentation to hospital. This information has been added to the case report.

3. What anesthesia was used for surgery? Was any hepato-toxic drugs used during or after surgery? Did that precipitate a liver failure in a metastatic liver?

RESPONSE: The patient's melanoma was resected under local anesthestic. From the author's knowledge he did not take any potential hepato-toxic medications. This information has been added to the case report.

4. CT scan figure of metastatic liver at second admission. It would be interesting if a rapid tumor growth has occurred in 3 weeks time. Alternatively, since autopsy has been performed, photo of the specimen is desirable.

RESPONSE: Abdominal imaging was planned for assessment of metastatic spread, however prior to obtaining diagnostic imaging the patient presented to hospital. Thus, a baseline CT scan prior to admission was not available. This information has been included into the case report.

RESPONSE: Autopsy and picture of the gross liver was obtained. The quality of the picture that is available is not contributory to the case report and is therefore not included.

5. Our patient's course was also remarkable for a profound TLS that was recalcitrant to aggressive life
support measures including a six hour course of hemodialysis. With multi-organ failure and extensive liver disease, this statement is far fetched and needs to be modified or better deleted. It is understandable to treat TLS when it occurs in isolation. But in this case with such advanced disease what was the purpose of such aggressive therapy?

RESPONSE: This line has been deleted from the paper. Our aggressive approach was undertaken to allow a definitive diagnosis of metastatic melanoma. While we expected that this was the case we felt confirmation was required and that an infectious etiology or lymphoma needed to be ruled out.

6. Have spontaneous tumor lysis syndrome been reported in solid tumor? How and why does such an event occur without any precipitating cause like therapy? Discuss on these issues.

RESPONSE: TLS has been reported to occur in melanoma, however following chemotherapy. No cases of spontaneous TLS secondary to malignant melanoma has been reported. Please refer to the second paragraph of the discussion.

7. Discussion and references should include other solid tumors (other than melanoma) which have had tumor lysis syndrome separating those that occurred after any therapy to those that occurred spontaneously.

RESPONSE: Please see paragraph 2 of the discussion for revisions accordingly.

8. More detailed case report and discussion to incorporate TLS, TLS in solid tumors, TLS which has occurred spontaneously etc.

RESPONSE: This has been added in paragraph 2 of the discussion.

Reviewer 2:

Because this condition is exceedingly rare, the simple description is not enough - the readers may wish to understand the possible mechanisms, and the point is the autopsy. Thousands of massive liver metastasis cases are regularly seen, but TLS is a very rare consequence (it is mainly associated with treated hematological malignancies). Therefore, the findings should be firmly established. If the cause of TLS in the given case is the massive destruction of melanoma cells, the vast majority of the tumor would be destroyed (interestingly, Fig. 1. shows florid tumorous mass without any sign of lysis). Another question would be the mode of the massive destruction of the tumor cells. Was it a result of necrosis or apoptosis? Was there any predisposing factor of tumor lysis? Was there any thrombosis or obstruction in the hepatic arteries/veins? The authors mention a significant elevation of LDH that may suggest a massive hepatic necrosis. How did the liver cells look like? Is it possible that the lysis syndrome was resulted from the massive destruction of hepatocytes instead of the tumor cells themselves? If so, what was the relationship between the tumor and the liver: was there any massive tumoral embolization in the hepatic vasculature?

RESPONSE: As per our response to reviewer 1, we agree that the case does not adequately establish the diagnosis of tumor lysis syndrome and the case report has been revised to exclude this conclusion (and therefore the issues surrounding TLS are less relevant).

Reviewer 3:

There was no tumor lysis syndrome and the title as well as the discussion of the paper should be corrected accordingly.

RESPONSE: We agree with the reviewer and the paper has been revised accordingly.

Reviewer 4:

The authors should provide an explanation or speculation of why they think TLS is the diagnosis, rather than simply a combination of sinusoidal hypoxia from tumor infiltration with liver failure and concomitant renal failure. The authors should also elaborate on why they think TLS occurred, as TLS in cases of malignant melanoma usually occurs after chemotherapy.
RESPONSE: We agree with the reviewers that tumor lysis syndrome has not been established in our case and it has been revised accordingly.