Author response to reviewers

Reviewer 1

Comment 1: Living donor liver transplantation is growing in popularity and alpha-1-antitrypsin deficiency screening should be incorporated into donor screening protocols: Authors may include this fact also in the discussion.

Response: We thank the reviewer for the potential to explore different aspects in our case report. We have made the following amendments within our manuscript "it is suggested that living-donor liver transplantations should be screened for underlying metabolic disorders (e.g. AATD) as they could pose safety issues to both donor and recipient" (pg. 10)

Comment 2: The authors may include the details of the SNP/genetic screening done on this patient, the DNA sequence or RFLP gel picture.

Response: Unfortunately, further genetic assessment in this patient was not available due to "*in vivo* degradation of the phenotype specimen".

Comment 3: Anti-a1-ATT immunofluorescence staining of liver and lung tissue will show the denatured protein aggregates inside the cells. This will further confirm the diagnosis and would make this report more attractive and useful for the readers.

Response: We have included a histopathological section of the patient sample, but unfortunately do not have access to an immunofluorescence sample as we do not perform AATD immunofluorescence at our hospital trust.

Comment 4: The authors also may include some more details about a1-ATT deficiency, genotypes and phenotypes and its common clinical presentations.

Response: We have included more detail relating to AATD, whilst not overburdening the text with excessive detail. We have made two changes to the text to help increase the detail regarding AATD, which can both be found on Pg. 10;

" There are approximately 123 single nucleotide polymorphisms affecting the gene[19]. The M allele accounts for over 95% of alleles in the general population, with other alleles including S and Z, accounting for 2-3% and 1% respectively[18]. The normal phenotype is denoted Pi-MM"

"AAT is normally excreted from hepatocytes where it may counteract the action of neutrophil elastase. Failed excretion can lead to pulmonary inflammation and proteolytic damage, which may manifest as COPD[25]. Other associated clinical manifestations of AATD can include panniculitis and vasculitis[19]."

Reviewer 2:

Comment 1a: Authors should mention the detail, which is important in occurrence of PHLF. Do you use ICG clearance test as a preoperative liver function evaluation?

Response: Thank you for your comments and taking the time to read through our work. We have added additional detail to what we believe caused our patients PHLF. "We believe that PHLF in our patient was due to several factors; mainly undiagnosed AATD disorder, neo-adjuvant chemotherapy, and extended liver resection". (Top paragraph of Pg. 10). We do not currently use ICG clearance.

Comment 1b: Would you please provide data of estimated blood loss, blood transfusions, operative time and duration of liver transection.

Response: In accordance with the parameters you have suggested we have added the recorded blood loss and blood transfusions (bottom of pg. 6). The overall operating time was 390 minutes. Unfortunately, we cannot provide details of liver transection time because it is not our routine practice to record that parameter.

Comment 1c: What is the liver resection criteria in your department?

Response: We consider liver resection if we can leave 30% functioning liver volume in post chemotherapy livers, 40% in patients with established cirrhosis/fibrosis, and 20% in normal liver. We have included this information on Pg. 10.

Comment 1d: Do you use the Pringle maneuver during liver transection. If so, please tell us the total duration of Pringle clamping time. Moreover, how do you transect the liver (CUSA or Kelly-crushing method)?

Response: Senior author of the paper (SA) does not use Pringle maneuver during liver resection. In this patient we did not use Pringle maneuver. Liver was transected using CUSA and Thunderbeat (Olympus ®). (Updated at the bottom of Pg 6.)

Comment 2: Is there any report of safe hepatectomy in AATD patients? If a patient had AATD, is hepatectomy suitable or contraindicated?

Response: It is difficult to comment on safety of hepatectomy in AATD patients as we could not find any case reports in the literature. However, we have included detail regarding the suitability of hepatectomy in patients with AATD (Pg. 11).

"In a situation where AATD is detected pre-operatively, we recommend avoidance of major liver resection as it will affect liver regeneration. We would recommend pre-operative liver biopsy and liver volumetric analysis before deciding whether or not to consider a patient for major liver resection. If the FLR is less than 40% then major liver resection should be avoided and measures should be taken to increase FLR prior to surgery (e.g. portal vein embolization). In our case, we would not have considered major liver resection if we were aware of his diagnosis prior to surgery. Especially since he received several cycles of neo-adjuvant chemotherapy.

Currently, there is no recommendation for AATD testing in patients undergoing major liver resection. To help prevent the development of PHLF as seen in our case, we recommend formal testing for AAT levels and AATD phenotyping, in all patients with a known history of COPD, heavy smoking history, or those with a strong family history undergoing major liver resection. If AATD is identified, we recommend avoidance of major hepatectomy (more than 4 segments), even if patients do not receive neo-adjuvant chemotherapy."

Comment 3: In the reference section, the data of PMID is not required.

Response: Thank you for taking the time to look over our references. However, we have decided to keep the PMID number based on the manuscript specifications sent to us, which detail "Please provide the PMID number, which is the serial number that roots the abstract for that publication into the PubMed index, and the CrossRef DOI® (Digital

Object Identifier) name, which is a unique string created to identify a piece of scholarly content in the online environment for each reference in the References section"

Reviewer 3:

Comment 1: Modify the title so that it reflects this is a case-report article

Response: We have updated our title to reflect that it is a case-report article "Delayed Diagnosis of Alpha-1-antitrypsin Deficiency Following Post-hepatectomy Liver failure: a case report"

Comment 2: state relevant literature (postoperative liver failure due to undiagnosed AATP deficiency)

Response: We have reviewed the literature extensively and we did not encounter any literature on post-operative liver failure due to undiagnosed A1ATD. So, we are unable to state any relevant literature.

Comment 3: Suggest potential management modification for a situation where the case condition is known/diagnosed preoperatively.

Response: Thank you for some interesting thoughts on our case, and we appreciate the time you have taken to review our paper. We have incorporated this comment with '*comment 2*' from '*reviewer 2*' (see above). Our answer addresses the issue of management options and suitability if AATD is diagnosed preoperatively, which both comments from the reviewers refer to. (Please see our answer to this question above).