Author's response to reviews

Title: Life-threatening acute acalculous cholecystitis in a patient with renal cell carcinoma treated by sunitinib: case report

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Author's response to reviews: see over
We thank both reviewers and editorial team for their speedy and thoughtful suggestions and comments and have revised the manuscript according to reviewers’ critiques.

**Responses to referee #1**

(1) **What risk factors did the patient have for acalculous cholecystitis?**

Multiple risk factors which include sepsis, immunosuppression, total parenteral nutrition, opiates, etc have been indicated in the patient with acalculous cholecystitis (*J Clin Gastroenterol* 2003; **36**:166-9). Our patient had no obvious risk factors. We added that information at page 6, line 19.

*What was the patient’s past medical history?*

We added the information for the past medical history at page 4, line 13.

(2) **How and why was the decision made to treat this patient with Sunitinib given she did not have metastatic disease? It needs to be made clear (if this is the case) that this was an adjuvant treatment prior to resection. Was an integrated assessment system used for risk stratification eg the UCLA (UISS) system?**

Since we have administered sunitinib to our patient as neoadjuvant setting in the same manner as Thomas AA (*J Urol* 2009; **182**: 881-886), we corrected following sentences, “has been administered in the perioperative period [1]. Although sunitinib” at page 4, line 4 and “For the purpose of downstaging of the tumor, sunitinib therapy (50 mg per day, 4 weeks on and 2 weeks off) was started in the neoadjuvant setting.” at page 4, line 17.

3) **The antivascular effects of Sunitinib are interesting – a recent paper by Aparicio- Gallego (Anticancer Drugs, 2011 Jan 22 (1) 1-8) pinpointed potential molecular causes of hypertension in Sunitinib treatment including endothelial dysfunction, altered NO metabolism, vascular rarefaction and so on. Perhaps more up to date references in the discussion on the microischemic effects of Sunitinib might help us understand better the adverse effect of acalculous cholecystitis.**
We investigated the latest article, amended the sentence at page 7, line 6 and added references [6]-[9].

4) A small box diagram of the Naranjo scale would be helpful

We made table 1 about the Naranjo scale of our patient.
Responses to referee #2

(1) There is a fair bit of repetition of text through the manuscript. Grammar corrections needs in several areas.

We corrected the repetition and grammar.

(2) It would be useful to comment on and see the CT images of the gall-bladder at the time of patient's initial presentation with the RCC, before Sunitinib therapy was commenced.

We newly added figure 2 that showed a normal gallbladder at the first visit in abdominal CT and the comment “Despite a normal gallbladder at the first visit (Fig.2),” at page 5, line 7.

(3) Is it possible that the cholecystitis is related the patient presenting with advanced renal malignancy (T4 disease with a suspicious liver lesion) as opposed to an association with Sunitinib - I feel the authors should comment on or at least acknowledge this.

We consider that the cholecystitis adverse event would be associated with sunitinib based on the following three reasons. First, the symptoms due to cholecystitis improved with discontinuation of sunitib. Second, Naranjo scale score for the present case was five, indicating a probable association of the cholecystitis with sunitinib. Third, while our patient has already had advanced renal malignancy, she did not indicate the symptoms due to cholecystitis at the first visit. This point was described at page 6, line 17.

(4) The authors have not mentioned /excluded other causes of deranged liver function tests in the manuscript, e.g. what other medications was the patient on? Stauffer syndrome, etc...

Because our patient did not have particular past history to be mentioned, we added the sentence, “She had no history of medication or smoking, and was a social drinker.” at page 4, line 13. We added the following sentence at page 6, line 19, “there were no risk factors including gallbladder stone, common bile duct stenosis and other hepatobiliary
diseases that could cause acute cholecystitis and deranged liver function.”

(5) Was the surgery carried out laparoscopically or open - how difficult was the intra-operative dissection? was there evidence of post-cholecystitis intra-operative pathology.

Open nephrectomy was performed. Severe adhesions around gallbladder and renal tumor have been identified and made the surgery difficult, suggesting that cholecystitis was severe. We corrected the sentence at page 5, line16.

(6) The authors should make reference to exactly what modalities they have used in the follow-up period to deem the patient recurrence free.

The patient was followed up using a computed tomography (CT). We added the following sentence, “identified by means of CT” at page 6, line 4.
Responses to editorial team

(1) Please replace the header 'Background' to 'Introduction.'

We replaced the header 'Background' to 'Introduction' in the abstract and case presentation sections.

(2) Please include the ethnicity of the patient in the abstract and case presentation sections of the manuscript.

We added “Japanese” at page 2, line 8 and page 4, line 12.

(3) Please replace dates found in the manuscript to the amount of time this occurred before the presentation of the case report.

We deleted the phrase “in July 2010” at page 4, line 12 and “in October 2010” at page 5, line 12 in prerevised manuscript and added the following phrase “After three months,” at page 5, line 14.

(4) Please include the author’s contribution section.

The author’s contribution section has been added according to your instructions.