Date: 7.11.2019

Re: Manuscript ID 52038: Acute cholecystitis? Think again. A case report and literature review of Gallbladder Tuberculosis

Dear Editor,

We are thankful to you and both reviewers for insightful critic and comments. We have enhanced the manuscript accordingly and enclosed below is the response to comments along with the highlighted changes made in manuscript. The changes made in the manuscript are coloured red.

Yours sincerely,

Dr Junnarkar Sameer P

Corresponding Author

Tan Tock Seng Hospital, Department of General Surgery, Singapore 308433

Contact: +65 63577807

Email: sp_junnarkar@ttsh.com.sg

Reviewer: 1

1. Please explain how would the case have been different if the TB was diagnosed before the surgery? Would the patient have needed TB meds then cholecystectomy or would the patients have gone to surgery anyway?

Response: Thank you for this pertinent question. Should TB be diagnosed before the surgery, the patient would be started on TB treatment immediately and also undergo cholecystectomy as per

the acute cholecystitis guidelines from the TG18 guidelines (Okamoto, K. , Suzuki, K. , Takada, T. et al. (2018), Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci, 25: 55-72. doi:10.1002/jhbp.516).

2. Realistically, is it possible to diagnose isolated TB of the gallbladder? Or do you expect these rare cases to always be diagnosed post operatively?

Response: Clinically, we believe it is not possible to diagnose isolated TB of the gallbladder unless there is a strong index of suspicion. We did not suspect isolated TB of the gallbladder as "the possibility of gallbladder TB was not a consideration in this patient with no significant past medical history and absence of immunosuppression", and "Gallbladder TB is a rare entity due to population vaccination and intrinsic resistance for tuberculous infections". Pre-operative CT imaging may show signs suggestive of TB, such as "heterogenous enhancement of the gallbladder may suggest caseating or liquefactive necrosis", but also requires an index of suspicion. Hence, we propose that these rare cases will usually be diagnosed post-operatively.

3. Please elaborate or spell out the G10 score in the sentence "The G10 operation score was 5". I suspect many readers would not be able to understand what this score is because they are not surgeons.

Response: Thank you for your comment. We have changed G10 to "10-point intra-operative gallbladder scoring system (G10)" with the reference (Sugrue M, Coccolini F, Bucholc M, Johnston A. Intra-operative gallbladder scoring predicts conversion of laparoscopic to open cholecystectomy: a WSES prospective collaborative study. World Journal of Emergency Surgery. 2019;14(1):12.)

4. Please consider renaming the title to "isolated gallbladder TB mimicking acute cholecystitis " or something similar. The current title: " Acute cholecystitis? Think again. A case report and literature review of Gallbladder Tuberculosis" does not read well at all to me.

Response: Thank you for your suggestion. We will change the title to "Isolated gallbladder tuberculosis mimicking acute cholecystitis: a case report and literature review".

Reviewer: 2

1. Did the patient ever get told of her diagnosis before discharge? If not it would be nice to more clearly state why pre-operative diagnosis is paramount.

Response: The patient was told of her diagnosis of gallbladder tuberculosis and was advised to follow-up in her home country for tuberculosis as stated in the manuscript "She was subsequently discharged and followed-up at a hospital in her home country due to financial and social reasons". Unfortunately, the patient did not want to stay in Singapore for further investigations and treatment for financial and social reasons.

2. Although generally well-written, there are a few grammatical issues that need to be addressed

Response: Thank you for your suggestions. We have rectified the grammatical errors and highlighted them in red.

Reviewer: 3

1. In the case, laparoscopic cholecystectomy was performed in the patient with 3 cm gall-bladder stone. But, the localization of the stone was not given. If ultrasound examination had been performed, it should have been described in the materials section along with the stone localization in the gall bladder.

Response: The gallbladder stone was found on CT imaging and after dissection of the gallbladder specimen. No formal ultrasound scan was performed for the patient and hence, is not described in the materials section.

2. Is TBC bacteria found incidentally or the main cause of this clinical symptoms?

Response: Thank you for your question. Mycobacterium tuberculosis was found incidentally on histology and AFB smear. Histology revealed acute on chronic cholecystitis.

3. It would be better to cite the study with the number of "Rana C, Krishnani N, Kumari N. Ultrasound -guided fine needle aspiration cytology of gallbladder lesions: a study of 596 cases. Cytopathology. 2016 Dec;27(6):398-406. doi: 10.1111/cyt.12296. Epub 2016 Mar 15."

Response: Thank you for the suggestion. We agree that fine needle aspiration cytology (FNAC) may aid in the diagnosis of gallbladder tuberculosis. However, FNAC is not routine in the investigation and management of cholecystitis. We have included this in the manuscript "Ultrasound-guided fine needle aspiration cytology of the gallbladder, although not commonly performed in clinical practice, may suggest the presence of gallbladder TB: multiple granulomas with inflammatory and multinucleated giant cells and a positive Ziehl-Neelsen stain (16)".

We have also added in a "Core Tip" section:

Core Tip

Isolated tuberculosis of the gallbladder is extremely rare due to its intrinsic resistance to tuberculous infections. We present a rare case of isolated gallbladder tuberculosis presenting as acute cholecystitis. Clinical examination revealed positive Murphy's sign. The patient underwent laparoscopic cholecystectomy within the same admission. Histology shows necrotizing granulomatous inflammation with rare acid-fast bacilli (AFB) was identified on Ziehl-Neelsen stain. This case highlights the multivariable clinical presentations of gallbladder tuberculosis. Clinicians should have a high index of suspicion for patients in endemic regions presenting with cholecystitis to obtain a pre-operative diagnosis.