

ROUND 1

List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Octreotide-induced acute life-threatening gallstones after vicarious contrast medium excretion: A case report" (ID: 62503). These comments were very helpful and beneficial to revise and improve our paper. We have examined your comments carefully and have made the appropriate corrections, which we hope will meet your approval. The main corrections and the responses to the reviewers' comments in the paper are as follows:

Responds to the reviewer 1:

1、 I would suggest if possible to do a scheme regarding octreotide effects on gallstone formation with all the described known pathways. Moreover, I would suggest also a scheme showing your hypothesis as described in order to be of more easy impact for the reader. I believe these minor revisions are the only necessary ones.

Response: In our core tip, we hypothesis when the contrast medium was excreted into the hepatobiliary system, which was retained for a long time and concentrated by octreotide, this may have changed the physicochemical properties of bile and decreased nucleation time, resulting in the formation of acute gallstones. Similar changes might have occurred simultaneously in the intrahepatic biliary tree, which was the cause of poor bile excretion, and led to intrahepatic cholestasis and jaundice. And in the conclusion, we point out when the patient is at high risk of ectopic excretion, octreotide should be used carefully to avoid the severe cholecystitis. Thanks for the suggestion, we have already made the corresponding changes in our paper.

Responds to the Reviewer 2:

1、 Major comment: The authors have hypothesized that octreotide and VCME were the main reasons for the early formation of gallbladder stones. However,

there are many reports in literature that fasting alone can cause gallbladder sludge. Especially in elderly patients, even fasting for 3 days has been reported to be a risk factor for gallbladder sediment formation. According to the authors, the patient seems to have continued fasting until d5-post-RAE. Fasting alone could be the sole reason for gallbladder stone formation, and it is unclear why this possibility was neglected. If the authors have any additional data that supports their claim, and that fasting was not the major reason for gallbladder stone formation, this should be clarified.

Response: Fasting is the high risk of sludge formation that induced by gall bladder hypotonicity and stasis. Although our patient also fasted, his diagnosis and treatment was completely different from that of a patient who fasted alone. He underwent enhanced CT examination and was subsequently treated with octreotide. When the contrast medium was excreted into the hepatobiliary system, which was retained for a long time and concentrated by octreotide, this may have changed the physicochemical properties of bile and decreased nucleation time, resulting in the formation of acute gallstones. Similar changes might have occurred simultaneously in the intrahepatic biliary tree, which was the cause of poor bile excretion, and led to intrahepatic cholestasis and jaundice. As a result, his biliary tract symptoms were worse than those of patients who fasted alone. We have already made the corresponding changes in our paper.

ROUND 2

Dear Editors and Reviewers: Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Octreotide-induced acute life-threatening gallstones after vicarious contrast medium excretion: A case report"(ID: 62503). These comments were very helpful and beneficial to revise and improve our paper. We have examined your comments carefully and have made the appropriate corrections, which we hope will meet your approval. The main corrections and the responses to the reviewers' comments

in the paper are as follow: 1.The phrase in the title "Octreotide-induced acute life-threatening gallstones", that we think it may be apposite for the relation between octreotide and gallstones is well-known. The difference in our case is that gallstone formation occurred after vicarious contrast medium excretion and the nucleation time of gallstones was short. 2.The phrase in the Core Tip "it changed the physicochemical properties of bile and decreased nucleation time, finally resulting in the formation of acute gallstones." was modified to "it might change the physicochemical properties of bile and decreased nucleation time, finally resulting in the formation of acute gallstones". We hope the response would meet the requirements of reviewer, and are looking forward to your positive response. Thank you very much for your great help and please accept our best wishes.