

Response to Reviewer:

Reviewer Name: Anonymous

Review Date: 2022-05-18 09:22

1. Title: I think "disappearance" is not fully correct. The biopsy was performed and this procedure evidently led to the described result. Please, consider changing the word to be more precise.

RESPONSE: Yes, exactly. We changed the title more precisely according to the case condition.

Title changed: Spontaneous expulsion of a duodenal lipoma after endoscopic biopsy: an unusual case report and literature review (page 1 title, in red)

AND "disappearance" changed to "expulsion" all the manuscript (in red).

2. Throughout the text: please, ensure that "lipocytes" is correct. Adipocytes seems more commonly used.

RESPONSE: Yes, appreciate reviewer's comments. We looked up in Mesh. The usage of "lipocytes" is a mistake. We change Lipocytes to adipocytes all the manuscript (in red).

3. Conclusion: Please, consider revision to be more precise. "This phenomenon" seems not suitable (may be, "this case..." is better?). The second part ("to reduce invasion and complications during treatment") is not based on the described data and needs to be confirmed in comparative trials. I suggest skipping this part of the sentence.

RESPONSE: Yes, we should pay attention to the accuracy of wording. Though we thought a deep biopsy or fenestration is necessary for the lipoma, the conclusion should be made based on comparative trials.

"this phenomenon" changed to "this condition" (page 2, line 37, in red)

The sentence "to reduce invasion and complications during treatment" has been deleted. And conclusion changed as "Deep biopsy could lead to spontaneous gastrointestinal lipoma expulsion. This might be the first step in lipoma diagnosis and treatment." (page 2, line 39-40, in red)

4. Cor tip: larger studies are necessary to make a conclusion on which treatment option is better. Probably, the choice of treatment may depend on the size, the depth and the placement of the lipoma. Lipomas are not lipocytes, but benign lesions please, revise the first sentence. The last sentence is not appropriate, as 1) the case of duodenal (only) lipoma was discussed, 2) the case can not prompt anyone to do anything and 3) in case of relatively small size of lipoma the outcomes may be better.

RESPONSE: We made revision of the "Core tips" according to the valuable advice as follows:

The spontaneous expulsion of the lipoma enlightens us the possibility of taking a deep biopsy as a fenestration in the first step as the diagnostic and therapeutic procedure. (Page 3, line 49-51, in red)

5. In regard to the main complaints, the subject could have duodenal motor disorder (like functional dyspepsia) or both, functional and lipoma-related. If available, please, provide the data of contrasted X-ray examination and more details on the dependence of the symptoms on the volume of ingested food.

RESPONSE: a) We detailed the symptoms in the “History of present illness”: The patient suffered early satiety and mild reflux, especially after greasy meals, without abdominal pain, melena, fever, or jaundice. The symptoms were moderate and paroxysmal, which affected his appetite. He reported no weight loss during the past half a year. There was no history of abdominal surgery (Page 4, line 70-73, in red).

b): We are sorry, but the contrasted X-ray examination haven't been performed on this patient.

6. Please, provide more details on the subject's demography and anthropometry.

RESPONSE: We added vital signs, temperature, weight, height, and BMI. Supplementary the details of the physical examination as follows:

On physical examination, the patient's vital signs were stable with a 37.2°C body temperature on admission. The subject's height was 170cm and weight was 80kg, with BMI 27.68 kg/m². No obvious abnormalities were observed regarding the pulmonary and cardiac examination. There was no tenderness, mass, unusual bowel sounds or Murphy's sign in the abdominal examination. No jaundice or superficial lymphadenopathy was observed. (Page 5, line 77-82, in red)

7. Imaging examination: please, specify that CT was performed with the use of contrast (as "without enhancement" is somewhat confusing).

RESPONSE: Yes, the statement of the sentence is not accurate. It was revised as: Contrast-enhanced computed tomography (CT) revealed a suspicious low-density lesion in the periampullary region without enhancement. (Page 5, line 89, in red)

8. If available, please, provide the data of histology (or, at least, stains used and the morphologist's report). In case if no confirmation by histology was obtained, there is a need for better description of the grounds for the version of lipoma. Could it be an inflammatory cyst of the duodenal mucosa (containing pus), for example?

RESPONSE: We reviewed the pathological section and added figures (Sudan stain is not available, because the specimen is formalin-fixed. And we use S-100 immunohistochemical marker instead): Microscopic examination showed a small amount of roundish adipocyte in the submucosa layer, expressing S-100. Tiny lipid droplets were observed in cell cytoplasm. The glands of epithelium were neatly arranged on top. The small fragments of biopsy compatible with a submucosal lipoma. (Page 6, line96-100, in red)

The sentence “Histologically, only the inflamed mucosa was observed” was deleted.

9. Treatment: please, add details whether the subject received treatment after procedure (for example, antisecretory drugs? prokinetics?). Where the haemostatic procedures performed after the biopsy?

RESPONSE: We added the treatment information in the “TREATMENT” part as: During endoscopy, the patient received neither resection nor haemostatic procedures after the biopsy. We prescribed prokinetics and proton pump inhibitor to relieve his symptoms. (Page 6, line 106-107, in red)

10. Final diagnosis is not appropriately described. Please, provide the grounds for the version

of lipoma.

RESPONSE: We have reviewed the pathological sections and the results were recorded as “Microscopic examination showed a small amount of roundish adipocyte in the submucosa layer, expressing S-100. Tiny lipid droplets were observed in cell cytoplasm. The glands of epithelium were neatly arranged on top. The small fragments of biopsy compatible with a submucosal lipoma. (Page 6, line96-100, in red)”. We believed that was the grounds for the version of lipoma.

11. Could you, please, add more details on the patient's complaints at the follow-up?

RESPONSE: Sure, details on the complains should be added: After the endoscopy, mild symptoms were occasionally occurred during the follow-up period, without medications. (Page 7, line119-120, in red).

12. Please, consider adding details on the equipment used for preparation this case (model, manufacturer, country of origin), if you suppose this relevant.

RESPONSE: The information of the equipment is added: The Ultrasound Processor and probe information: OLYMPUS EUS EU-ME2, UM-DP12-25R, 12MHz radial miniprobe, Olympus Corporation, Tokyo, Japan (Page 2, line 33-34, in red) (Page 5, line 90-91, in red)
The forceps information: Micro-Tech Co. Ltd., Nanjing, China (Page 6, line 95-96, in red)

13. The format of the manuscript is not within the Journal's standards, please, revise.

RESPONSE: We download “Format_for_Manuscript_Submission-Case_Report” file from WJG, and take it as reference. Changes made as followings:

- a) Titles of “*Chief complaints*”, “*History of present illness*”, “*History of past illness*”, “*Physical examination*”, “*Laboratory examinations*”, “*Imaging examinations*” were bolded. (Page 4-5, in red)
- b) Move the abbreviations to the last part of the manuscript.
- c) Change the title of “Ethics Statement” to “Informed consent statement” (Page 13, line 278, in red)
- d) Delete the “Data Availability Statement” part.

14. The manuscript requires language polishing

RESPONSE: We have native expert polished language of the manuscript. Certification is in the attachment.

Reviewer Name: Anonymous

Review Date: 2022-04-10 20:27

1. Page 2 – to reduce invasion? What kind of invasion? Perhaps invasiveness of the procedure. Lipomas are benign and do not exhibit an invasive growth pattern.

RESPONSE: Yes, the statement of the sentence is not accurate. We mean the deep biopsy or fenestration as first step could reduce the size of lipoma to decrease complications of obstruction, bleeding, and necrosis. And minished volume reduced the difficulty and complications of endoscopic procedure for the required lipoma. The sentence “to reduce invasion and complications during treatment” has been deleted. And conclusion changed as “Deep biopsy could lead to spontaneous gastrointestinal lipoma expulsion. This might be the first step in lipoma diagnosis and treatment.” (Page 2, line39-40, in red)

2, Lipomas are benign and do not exhibit an invasive growth pattern. - Not all keywords are MESH indexed.

RESPONSE: We rewrite the keywords and look them up in MESH.

Lipoma: MeSH Unique ID: D008067

Biopsy: MeSH Unique ID: D001706

Adipose Tissue: MeSH Unique ID: D000273

Duodenal Neoplasms: MeSH Unique ID: D004379

3. Core tip –lipomas are composed of mature adipocytes. A lipoma is not a mature lipocyte. - Also – I would suggest using the same terminology as the WHO book on soft tissues. Meaning – adipocytes and not lipocytes.

RESPONSE: Yes, appreciate reviewer’s comments. We looked up in WHO book. The usage of “lipocytes” is a mistake. We change Lipocytes to adipocytes all the manuscript (in red).

5. The spontaneous disappearance of the lipoma prompts us to perform a deep biopsy as a fenestration for diagnosis as well as treatment with minimal invasion and complications, particularly in cases where the lesion is relatively large or located in the small intestine. – this sentence is not entirely understandable. I believe the usage of the word “prompts” is not adequate. This “event / spontaneous disappearance of the lipoma” leads you to believe that such a course of action (deep biopsy) is most adequate. It is impossible to extrapolate a case report into a “state of the art recommendation”.

RESPONSE: Yes, we should pay attention to the accuracy of wording. Though we thought a deep biopsy or fenestration is necessary for the lipoma, the conclusion should be made based on comparative trials.

The sentence “to reduce invasion and complications during treatment” has been deleted. And conclusion changed as “Deep biopsy could lead to spontaneous gastrointestinal lipoma expulsion. This might be the first step in lipoma diagnosis and treatment.” (page 2, line 39-40, in red)

6. Usage of the word submucosal. Perhaps the authors should choose one term: either

subepithelial or submucosal.

RESPONSE: Thank you for advice on precise wording. We change “subepithelial” to “submucosal” all the manuscript (in red).

7. I believe that a histology image of the biopsy (preferably HE + sudan if there is any viable material) should be added.

We reviewed the pathological section and added figures (Sudan stain is not available, because the specimen is formalin-fixed. And we use S-100 immunohistochemical marker instead): Microscopic examination showed a small amount of roundish adipocyte in the submucosa layer, expressing S-100. Tiny lipid droplets were observed in cell cytoplasm. The glands of epithelium were neatly arranged on top. The small fragments of biopsy compatible with a submucosal lipoma. (Page 6, line96-100, in red)

8. Outcome and follow-up – were more biopsy samples taken? If so, what did the histologic examination show? - What happened to the patient after the 12th day? Was he immediately discharged?

RESPONSE: We further detail the “Outcome and follow-up”: only once deep biopsy. During endoscopy, the patient underwent neither resection nor hemostatic procedures after the biopsy. Prokinetics and proton pump inhibitor were prescribed to relieve the symptoms. (Page 5, line 106-107, in red).

We reviewed the histology. Microscopic examination showed a small amount of roundish adipocyte in the submucosa layer, expressing S-100. Tiny lipid droplets were observed in cell cytoplasm. The glands of epithelium were neatly arranged on top. (Page 6, line96-100, in red). The sentence “Histologically, only the inflamed mucosa was observed” was deleted.

Because the patient insisted on the removal of the lesion. Because the patient was not local, he was ready to get himself admitted to the hospital after 12 days. After the endoscopy which had the finding of spontaneous expulsion, we discharged him and keep follow-up.

9. I believe the readers would appreciate a graphical depiction of the different endoscopic resection techniques.

RESPONSE: We added a figure (figure 3) to describe the different endoscopic procedures. (Page 17, line 312-315)

10.I lipoma was found spontaneously disappeared – was found gone ... Or was no longer present. Also – I would perhaps add that - macroscopically the site appeared to be inflamed / or displayed signs of inflammation and scarring. Again, a histological image would be appreciated.

RESPONSE: We appreciate the advice sincerely. According to the follow-up endoscopy and EUS, we believe that the lipoma was no longer present. And we add the sentence “macroscopically the site appeared to be inflamed / or displayed signs of inflammation and scarring.” (Page 6, line 117-118, in red). Microscopic examination showed a small amount of roundish adipocyte in the submucosa layer, expressing S-100. Tiny lipid droplets were observed in cell cytoplasm. The glands of epithelium were neatly arranged on top. (Page 6,

line96-100, in red) (figure F, G)

11.Regarding the statement that this is the third reported case of spontaneous expulsion after biopsy ... If the authors want to keep this claim, I suggest including a search algorithm in 2 sentences (used keywords, database, for so many years, so many results). Otherwise, these claims are too vague. Some potentially useful literature:

RESPONSE: We appreciated your supplementary references. Wrong search algorithm led us to the statement of "this is the third reported case". We revised it as "There were a few cases of spontaneous expulsion after biopsy of GI lipoma" (Page 7, line164, in red)

We searched the PUBMED with algorithm: ((lipoma [Title]) AND (biopsy [Title/Abstract])) AND (gastrointestinal tract[Title/Abstract] OR gastric[Title/Abstract] OR colonic[Title/Abstract] OR intestinal[Title/Abstract] OR duodenal[Title/Abstract]) from 1975 to 2022: 24 results and abstract were carefully read, showing 4 reports related to similar condition (manuscript ref 21-24), including reviewer helpful literatures.

Revision reviewer's comment:

1. Congratulations to the authors with the great job done! The manuscript is now significantly improved. The questions raised have been appropriately answered. Thanks a lot! I appreciate the very careful review from the reviewers. The improvement cannot be made without your important advice! 2. Abstract: "Case summary" and "Conclusions" are identical.

RESPONSE: In the manuscript, the abstract is as follows: Abstract BACKGROUND Gastrointestinal lipomas are benign submucosal tumors of mature adipocytes that arise mainly in the colon and stomach, sometimes in the ileum and jejunum, and rarely in the duodenum. Patients with symptomatic lipomas require endoscopic or surgical treatment. Spontaneous expulsion of lipomas after biopsy is a rare condition that has limited case reports. CASE SUMMARY A 56-year-old man presented to our hospital with intermittent postprandial epigastric fullness. Esophagogastroduodenoscopy (EGD) revealed a 10-mm soft yellowish submucosal lesion with the "pillow sign," located in the second portion of duodenum. Endoscopic ultrasonography (EUS) using a 12-MHz catheter probe showed a hyperechoic, homogenous, and round solid lesion (OLYMPUS EUS EU-ME2, UM-DP12-25R, 12-MHz radial miniprobe, Olympus Corporation, Tokyo, Japan). Deep biopsy was performed using the bite-on-bite technique with forceps. Histological examination was compatible with submucosal lipoma. The lesion spontaneously expelled 12 days after the biopsy. Follow-up EUS performed after 2 months confirmed this condition. CONCLUSION Deep biopsy could lead to

spontaneous gastrointestinal lipoma expulsion. This might be the first step in lipoma diagnosis and treatment. (Page 2, line 21-42, as it described in the "Answering reviewers")

3. I would suggest transferring the description given in "Final diagnosis" to "Imaging examinations" and added Duodenal lipoma (probably, with more details) to the Final diagnosis.

RESPONSE: the description of pathology has transferred to the "Imaging examinations" part (Page 4`5, Line 94-98, in blue). We have added Duodenal lipoma to the Final diagnosis. (Page 5, Line 101, in blue)

4. Please, note, that a patient can hardly report bleeding, perforation, or any other complications (probably, it is better to say that these outcomes were not observed) - please, revise.

RESPONSE: Exactly! We should pay attention to the precise wording! The sentence revised as: The complications as bleeding, perforation, or infection were observed in the patient. (Page 5, Line 101-102, in blue)

5. Outcome and follow-up: "The patient reported milder symptoms and fewer episodes after prescription." - the phrase is senseless, please, revise or delete.

RESPONSE: We deleted the sentence.

6. Acknowledgements: please, check that all the names start with the Capitals. As there are several authors, it would be better to put down who exactly expresses the gratitude to Dr. Chen and whose husband is really beloved and thanked (however, it is none of my business, and then, please, use plural - we and our, instead)). These comments in no way diminish scientific quality of the paper and may be easily corrected.

RESPONSE: The names start with the Capitals have been checked. The manuscript was revised all the time by Yimiao Zhu. So, acknowledgements revised to: "Yimiao Zhu would extend her sincere gratitude to Yuan Chen for his careful review of the pathology, valuable suggestions, and inspiring advice of the case. Special thanks should go to her beloved husband for his continuous support and encouragement." (Page 9, Line 193-195, in blue)