June, 3th, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 18061-Review.docx).

Title: Perforated appendiceal diverticulitis associated with appendiceal neurofibroma in neurofibromatosis type 1

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 18061

We appreciate your kind consideration of our manuscript (the comments of the reviewers are underlined). The manuscript has been improved according to the suggestions of reviewers. The replies to each point of the reviewers are attached below and we now believe that we have satisfactorily addressed the points.

We hope that this manuscript would meet your approval for publication in the World Journal of Gastroenterology, and we look forward to hearing from you soon.

Sincerely yours,

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Reply to the editor:

We added "Ethics approval" statement, "Informed consent" statement, "Conflict of interest" statement, and a "Comments" section as required. We also attached an "Audio Core Tip" file. In addition, mistakes on grammar, spelling, and references have been corrected. The format has been updated. We kindly ask for an exemption from providing a certificate letter from a professional English language editing company.

Reply to the first reviewer:

Reviewer 1 Comments:

1)

Thank you for giving me a chance to review this study. I really appreciate your efforts to contribute the paper. I review your manuscript: Perforated Appendiceal Diverticulitis Associated with Appendiceal Neurofibroma in Neurofibromatosis Type 1. I inform this paper can passed under my authority.

Reply:

Thank you for your kind comment about our work.

Reply to the second reviewer:

Reviewer 2 Comment:

1)

1. In the article the reason for hospitalization of patient for 23 days should be emphasized.

Reply:

We agree with your opinion that the reason for a long hospitalization after the surgery should be emphasized. During the surgery, drainage tubes were placed in the rectovesical pouch and the abscess cavity, respectively. Drainage from the rectovesical pouch was serous soon after the operation, but in a large amount. The tube was removed six days after the surgery, when the amount of drainage decreased. However, even one week after the surgery, the drainage from the abscess cavity remained purulent, leading to the diagnosis of a remnant abscess. The conservative treatments of antibiotics and drainage via the tube were continued because the condition of the patient was stable without abdominal pain or fever. The amount of purulent drainage gradually decreased, and fifteen days after the surgery, the fluoroscopy revealed the size of abscess cavity was small. Therefore, we started to remove the drainage tube two centimeters per day. The tube was finally removed twenty-two days after the surgery. The patient was discharged from the hospital twenty-three days after the surgery. To address this issue, we modified the sentences.

(On the page 6 line 25 in the previous version), from:

"Due to a remnant abscess, he received conservative treatments using antibiotics. His conditions improved, and he was discharged 23 days after the surgery."

(On the page 5 line 13 in the revised version), to:

"During the surgery, drainage tubes were placed in the rectovesical pouch and the abscess cavity, respectively. Drainage from the rectovesical pouch was serous, and the tube was removed six days after the surgery, when the amount of drainage decreased. However, even one week after the surgery,

the drainage from the abscess cavity remained purulent, leading to the diagnosis of a remnant abscess. The patient received the conservative treatments of antibiotics and drainage, and the amount of the exudates via the tube gradually decreased. The tube was removed twenty-two days after the surgery. He was discharged twenty-three days after the surgery."

2)
2. Introduction and discussion parts must be extended.

Reply:

Thank you for your thoughtful suggestion. Following your suggestions, we have extended the introduction and the discussion. We believe this modification allowed us to review the abdominal manifestations in neurofibromatosis type 1 in detail, and made the abstract and "Core tip" more informative.

In the introduction, we added the following sentences.
"Neurofibromatosis type 1 (NF-1) is one of the most common inheritable diseases[1]. It is a neurocutaneous disorder that possesses a high risk of multiple tumor formation[2]. It can involve intraabdominal organs as well as the nervous system and the skin[1, 2]." (On the page 4 line 11 in the revised version)

In the discussion, we added the following sentences.
"NF-1 can cause various abdominal manifestations. Abdominal neurofibromas can arise from the esophagus to the anorectum, and also in the associated peritoneal and mesenteric soft tissues[1]. Other than neurofibromas, gastrointestinal stromal tumors and neuroendocrine tumors may occur[17]. An early diagnosis is important, considering the risk of malignancy and complications, such as hemorrhage, obstruction, and perforation[17,18]. However, a recent report indicates abdominal manifestations of NF-1 rarely come into the mind of clinicians due to a lack of knowledge about their frequency and wide clinicopathological spectrum[1]. Awareness of abdominal manifestations holds great importance in the management of NF-1, as it has been shown that a considerable number of patients with NF-1 develop abdominal tumors [17]. " (On the page 7 line 1 in the revised version)

3)
3. Explanations about incision type for laparotomy and whether drainage tube was placed or not would make article more qualified.

Reply:

We agree with your view. In the surgery, a lower midline incision was performed because we were afraid that pararectal incision or Lanz incision, usually performed incisions in appendectomy in Japan,

would not offer a good view to successfully drain the abdominal abscess. Drainage tubes were placed in the rectovesical pouch and the abscess cavity, respectively. To address this issue, we added the following sentences.

"A lower midline incision was performed to successfully drain the abdominal abscess." (On the page 5 line 10 in the revised version)
"During the surgery, drainage tubes were placed in the rectovesical pouch and the abscess cavity, respectively." (On the page 5 line 13 in the revised version)

Reply to the third reviewer:

Reviewer 3 Comment:

1)

The authors describe a case of ruptured appendiceal diverticulitís in a patient with appendiceal neurofribroma and neurofibromatosis type 1 and reviewed the literature regarding appendiceal diverticulitis and ANF. #1 page 4: The conclusion within the abstract section should be less strong ('might be...' instead of 'is a complication...') because there is just one case reported and as discussed later coincidence cannot be excluded.

Reply:

We agree with your view and accordingly we have modified the sentence.

(On the page 4 line 15 in the previous version), from:
"This case suggests that appendiceal diverticulitis is a complication of appendiceal involvement of NF-1, and that it occasionally ruptures even in the absence of intense abdominal pain. "
(On the page 3 line 18 in the revised version), to:
"This case suggests that appendiceal diverticulitis might be a complication of appendiceal involvement of NF-1, and that it occasionally ruptures in the absence of intense abdominal pain."

2)

#2 page 5: As these are really rare cases the last sentence of the 'core tip' regarding the clinician's awareness of appendiceal perforation in patients with NF-1 should be deleted from the revised manuscript.

Reply:

We appreciate your advice. We have deleted the phrase you indicated, and modified the sentence, also considering the suggestions of other reviewers

(On the page 5 line 1 in the previous version), from:
"This patients presents with NF-1 and developed an ANF, complicated with appendiceal diverticulitis to highlight the possible association of appendiceal diverticulitis and ANF in NF-1, and to enhance the clinician's awareness of appendiceal perforation in NF-1."
(On the page 5 line 3 in the revised version), to:
"This patient presented with NF-1 and developed an ANF, complicated with appendiceal diverticulitis,

which highlights the possible association of appendiceal diverticulitis and ANF in NF-1. This case could be used to enhance clinicians' awareness of abdominal manifestations in NF-1."

3)
#3 page 6: The normal range of CRP in the testing laboratory should be mentioned in the revised manuscript to allow the reader for better estimation of the value 7.26 mg/dL.

Reply:
Thank you for your kind comment. Following your advice, we have modified the sentence.

(On the page 6 line 20 in the previous version), from:
"Serum levels of C-reactive protein were 7.26 mg/dL."
(On the page 5 line 7 in the revised version), to:
"Serum levels of C-reactive protein were 7.26 mg/dL (normal value: < 0.3mg/dl)."

4)
#4 page 7: As the coincidence of diverticulitis and ANF cannot be excluded the first sentence of the discussion should be revised writing 'suggests' instead of 'shows'.

Reply:
We agree with your suggestion and accordingly we have modified the sentence.

(On the page 7 line 10 in the previous version), from:
"This case shows that appendiceal diverticulitis may be a complication of ANF in NF-1."
(On the page 6 line 1 in the revised version), to:
"This case suggests that appendiceal diverticulitis may be a complication of ANF in NF-1."

5)
#5 page 8: The last sentence of the discussion does not add any new information and therefore might be deleted from the revised manuscript.

Reply:
We respect your advice. We have deleted the sentence indicated, while we have added the following sentences as a conclusion, based on the modifications we have made in the revised manuscript.

(On the page 8 line 13 in the previous version), from:
"In conclusion, an ANF in NF-1 can be complicated with appendiceal diverticulitis, which might ruptures even in the absence of intense abdominal pain.
(On the page 9 line 4 in the revised version), to:
"In conclusion, this case suggests that appendiceal diverticulitis might be a complication of appendiceal involvement of NF-1, and that it occasionally ruptures even in the absence of intense abdominal pain.

Clinicians should recognize that NF-1 can cause various abdominal manifestations."

Reply to the fourth reviewer:

Reviewer 4 Comment:

1)

Thank you for the opportunity to read this paper: first of all, I would like to underline it is a well written paper but " What is the message for the reader?" The association between ANF and appendiceal diverticulitis seems not of great importance and, in my opinion, the paper it is suitable for publication is a journal dedicated to case report.

Thank you for addressing this critical issue. We see your concern, but all case studies could hold some importance. With rigorous effort, we were unable to find any similar reports or descriptions, so we felt that this case was quite rare and worthy of reporting. At this stage, we are not positioned to judge if the case is just rare in clinical settings or if this case represents other patients. Since we presume that this case could be representative of others, we have prepared this report to enhance awareness in other clinicians.