28-Jan-2023

Dear Dr. Peter Schemmer

Editor-in-Chief & Co-Editor

World Journal of Gastrointestinal Surgery

Thank you for inviting us to submit a revised draft of our manuscript entitled "Clinical features of acute esophageal mucosal lesions and reflux esophagitis Los Angeles classification grade D: a retrospective study". We also appreciate the time and effort you and each of the reviewers have dedicated to providing insightful feedback on ways to strengthen our paper. Thus, it is with great pleasure that we resubmit our article for further consideration. We have incorporated changes that reflect the detailed suggestions you have graciously provided. We also hope that our edits and the responses we provide below satisfactorily address all the issues and concerns you and the reviewers have noted.

To facilitate your review of our revisions, the following is a point-by-point response to the questions and comments delivered in your letter dated 24-Jan-2023.

Reviewer #1

The authors compared the clinical features of acute esophageal mucosal lesions (AEMLs, n=105) and LA-D reflex esophagitis (n=48) using a single-center retrospective study. The results showed significantly different results, indicating that the two diseases may be attributed to different pathologies. The results were very helpful for clincal practice, and it is recommended to supplement the etiology, such as the proportion of eosinophilic esophagitis, acute reflux, drug-related, etc. in AEMLs patients.

Response:

We fundamentally agree with the reviewer's appraisal. Eosinophilic esophagitis and acute reflux esophagitis due to obstruction by a tumor or ileus were originally excluded, and this is clearly stated in the METHODS for clarity. The exclusion criteria have been amended as follows:

> "Emergency upper endoscopy was defined as endoscopy performed within 24 hours of the request. We included patients with diffuse circumferential mucosal injury of the esophagus and excluded patients with corrosive

esophagitis, radiation esophagitis, infectious esophagitis, eosinophilic esophagitis, esophageal pemphigoid, and systemic sclerosis. We also excluded obstructive symptoms caused by tumors or ileus or post-upper gastrointestinal tract surgery." (page 6, 1st paragraph)

Reviewer #2

·This restrospective study is aimed at comparing endoscopic and pathophysiologic mechanisms of two conditions, i.e. acute esophageal necrosis (i.e. acute esophageal mucosal lesions) and grade D erosive esophagitis. It is already known that these endoscopic findings actually reflect, in the vast majority of cases, two different conditions. Acute esophageal necrosis (AEN), commonly referred to as "black esophagus", is a rare clinical entity arising from a combination of ischemic insult seen in hemodynamic compromise and low-flow states, corrosive injury from gastric contents in the setting of esophago-gastroparesis and gastric outlet obstruction, and decreased function of mucosal barrier systems - reparative mechanisms -present in malnourished and debilitated physical states. AEN may arise in the setting of multiorgan dysfunction, hypoperfusion, vasculopathy, sepsis,

diabetic ketoacidosis, alcohol intoxication, gastric volvulus, traumatic transection of the thoracic aorta, thromboembolic phenomena, and malignancy. On the other hand, grade D erosive esophagitis is the most severe stage of esophageal inflammation due to reflux disease. Given these different underlying mechanisms, results from the present study seem not to provide brand new data and are in line with those currently available.

Response:

Reviewer 2 considers that the present study compares acute esophageal necrosis (AEN) with reflux esophagitis grade-D (RE-D) and that AEN is not novel as many studies have been reported. However, our study compared RE-D with a new disease group such as acute esophageal mucosal lesion (AEML), and not with AEN. AEML consists of non-black and black esophagus (≒AEN). Some reports suggest that severe cases of non-black esophagus are black esophagus, and it is reasonable to consider them as a group of diseases because their clinical features are similar. However, AEML is not well recognized and there are few studies on it. Our study aims to reveal the clinical features of AEML by comparing AEML with RE-D, which is a well-known clinical condition. Our study showed that although AEML and RE-D have similar endoscopic features, they have very different

characteristics, and the results suggest the need to change treatment and follow-up. Thus, we consider this study to be highly significant with novel regulations.

·Some other issues need to be pointed out: • Inclusion criteria: patients with systemic sclerosis, esophageal tuberculosis and esophageal pemphigus should be excluded

Response:

Systemic sclerosis and pemphigus esophagus were originally excluded and are clearly stated in the exclusion criteria as follows.

> "Emergency upper endoscopy was defined as endoscopy performed within 24 hours of the request. We included patients with diffuse circumferential mucosal injury of the esophagus and excluded patients with corrosive esophagitis, radiation esophagitis, infectious esophagitis, eosinophilic esophagitis, esophageal pemphigoid, and systemic sclerosis. We also excluded obstructive symptoms caused by tumors or ileus or post-upper gastrointestinal tract surgery." (page 6, 1st paragraph)

・Was concomitant anti-coagulant therapy carefully assessed? This is relevant being an effective protective factor against arise of AEN and concomitant favouring factor of bleeding.

Response:

We also believe this information is important. Antithrombotic drugs are mentioned in **Table 1**.

・Patients with cirrohosis and previous variceal band ligation should be excluded

Response:

Not enough information on EVL for esophageal varices has been obtained. This point is noted in the limitations as follows.

> ''This study had some limitations. First, it was an observational study, and some of the possible information related to the outcomes, such as the duration of PPI administration and the history of treatment of varices with EVL, was not fully obtained. However, this is the largest study of AEML, adopting the more idealistic RE-D as a comparison. As a result, it may be possible to evaluate outcomes that could not be obtained in previous studies, such as the occurrence of stenosis. Second, the differences between AEML and RE-D in terms of endoscopic findings are not yet definitive. Although the present study was based on a previous report, further investigation is warranted.'' (page 11, 2nd paragraph)

·Gastric and duodenal ulcers were more frequent in patients with AEML but it is not clear length, duration and adherence to concomitant PPI treatment in all patients

Response:

Information on the duration of PPI use was difficult to obtain because it was not available prior to admission. This point is also mentioned in the limitations as follows.

> ''This study had some limitations. First, it was an observational study, and some of the possible information related to the outcomes, such as the duration of PPI administration and the history of treatment of varices with EVL, was not fully obtained. However, this is the largest study of AEML, adopting the more idealistic RE-D as a comparison. As a result, it may be possible to evaluate outcomes that could not be obtained in previous studies, such as the occurrence of stenosis. Second, the differences between AEML and RE-D in terms of endoscopic findings are not yet definitive. Although the present study was based on a previous report, further investigation is warranted.'' (page 11, 2nd paragraph)

·Unexpectedly, no esophageal stenosis followed healing of grade D esophagitis: how many patients underwent a 6-months follow-up?

Response:

Basically, we followed the patients up after 6 months whenever possible, except for those who died. In all, 80% or more of the cases were followed up.

・Please consider to carefully revise the entire manuscript for syntax and several types.

Response:

We requested English proofreading again and made corrections.

Sincerely,

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