

## ANSWERING REVIEWERS

13<sup>th</sup> of November 2012

Dear Editor,

Please find enclosed the edited the full-text manuscript in Word format

**Title:** *Cytomegalovirus-associated gastric ulcer: A side effect of steroid injections for pyloric stenosis*

**Author:** Hirohito Mori, Shintaro Fujihara, Noriko Nishiyama, Hideki Kobara, Makoto Oryu, Kiyohito Kato, Kazi Rafiq, Tsutomu Masaki

ESPS Manuscript NO: 632

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated
2. Revision has been made according to the suggestions of the reviewer

### Reviewer 1

Minor revision (CMV 632)

In this paper, Hirohito Mori et al. describe CMV-associated gastric ulcer due to side effect of local TA injection after treatment of an ESD ulcer floor in a non-compromised host. This is an interesting paper presenting a rare case report that is also of clinical importance regarding ESD. However, the following revisions are required to produce a paper suitable for publication.

#### COMMENT (1)

In the present case, ganciclovir was not administered. The reasons should be described.

#### RESPONSE

As you pointed out, we didn't mention the reason why ganciclovir was not administered. As the patient wasn't a compromised host and had no other underlying disease, we thought the CMV activity of the ulcer floor was limited and focal. The CMV ulcer was occurred under focal immunosuppressive condition by TA. We considered after TA effect would subside about for 14 days, the CMV activity would decrease and the ulcer healed. But it was necessary for us to follow up the ulcer by frequent endoscopy. Actually we performed follow up endoscopy at POD12, 20 and 30 and confirmed negative conversion of CMV by serology test and histopathological examination. We revised and added some sentences (Page 4, line12).

#### COMMENT (2)

Most CMV-related lesions of the digestive tract develop on the basis of a systemic immunosuppressive state. In this patient, was such an underlying disease absent truly?

The patient's background factors should be presented in detail.

RESPONSE

As you pointed out, we didn't mention the basis of a systemic immunosuppressive state of this patient. We revised and added some sentences (Page 4, line5) as follows:

As routine pre-ESD examination, we conducted serology test, electrocardiogram, respiratory function test, abdominal ultrasound examination and computed tomography. These results indicated no underlying disease.

COMMENT (3)

Can you conclude that the local injection of a steroid is an etiological factor for CMV-associated ulcers? The reasons should be described. For example, the reasons why short-term local steroid injection leads to the reactivation of CMV should be presented.

RESPONSE

Yes, we can possibly conclude that the local steroid injection is an etiological factor for CMV-associated ulcers. That's why the ulcer located at the center of the post-ESD artificial ulcer floor which was limited and local area. In general, in compromised host, CMV-related ulcers might make multiple lesions in digestive tract. Hence, this CMV ulcer might occur under focal immunosuppressive condition by TA.

We revised and added some sentences (Page 6, line 2) as follows:

In general, in compromised host, CMV- related ulcers might make multiple lesions in digestive tract. In this case, the ulcer located at the center of the post-ESD artificial ulcer floor which was limited and local area under focal immunosuppressive condition by TA.

In conclusion, the local steroid injection might be an etiological factor for CMV-associated ulcers.

COMMENT (4)

Are there any problems regarding the selection of local steroid injection or protocol (selection of administration, dose, site, or period)?

RESPONSE

As we mentioned our previous report "**Mori H**, et al. Local steroid injection into the artificial ulcer created by endoscopic submucosal dissection for gastric cancer: prevention of gastric deformity. *Endoscopy*. 2012; **44**: 641-8", we conducted local steroid injection into post-ESD artificial ulcers to 21 patients and analyzed them according to the protocol, there were no complications. So, this case was the first case of CMV-associated ulcer development related to the side effects of local steroid injection following ESD.

We revised and added some sentences (Page 5, line 10) as follows:

As our previous report <sup>[12]</sup>, we conducted local steroid injection into post-ESD artificial ulcers to 21 patients and analyzed them according to the protocol, there were no complications. So, this case was the first case of CMV-associated ulcer development related to the side effects of local steroid injection following ESD.

COMMENT (5)

It is described that this is the first case of CMV-associated ulcer development related to the side effects of local steroid injection following ESD. However, is the local injection-related reactivation of CMV rare? Are there any reports on the reactivation of CMV associated with local steroid injection in other fields (for example, in the oral cavity or skin)?

## RESPONSE

In dermatological field, we can find out some reports about Herpes Simplex Virus (HSV) related worsening ulcers after applied steroid cream. But in other fields, there are no report about CMV-associated ulcer development related to the side effects of local steroid injection.

### **Reviewer 2**

In this case report, the authors reported a case of a cytomegalovirus infection-induced ulcer related with local injection of triamcinolone acetonide after endoscopic submucosal dissection (ESD). As authors suggested this case report may be rare, and this report is interesting. But this version seems to have any problems.

Major comments:

COMMENT1. I don't know why authors performed endoscopy on day 12 after ESD.

## RESPONSE

As you pointed out, we didn't mention about it. As our previous report "**Mori H, et al.** Local steroid injection into the artificial ulcer created by endoscopic submucosal dissection for gastric cancer: prevention of gastric deformity. *Endoscopy*. 2012; **44**: 641-8", we conducted local steroid injection into post-ESD artificial ulcers on POD5 and POD12. That's because the proliferation of fibroblast begins at about five days after wound injury, therefore, we injected TA into post ESD ulcers on POD 5 and 12. In this, we also planned to conduct local steroid injection on POD 12, but we found out CMV induced deeper ulcer. So we stopped TA injection. As routine post-ESD ulcer follow up examination, we performed endoscopy on day 12 after ESD.

COMMENT2. Didn't patients have any symptom related with cytomegalovirus infection-induced ulcer? Most ulcerative colitis or Crohn's disease case with cytomegalovirus infection-induced ulcer has abdominal pain, diarrhea and fever.

## RESPONSE

We agree on your comment. Probably, the ulcer was rather small (about 8-10 mm in diameter) to come down with these symptoms. Moreover, we detected and treated the ulcer a little earlier. We think that's why the patient didn't have any symptom related with cytomegalovirus infection-induced ulcer.

COMMENT 3. How about use of acid inhibitory drugs? Cytomegalovirus infection may relate with use of PPI/H2RA. If so, please add comments of association with infection and drug use.

### RESPONSE

As you pointed out, administration of PPI/H2RA might have effects to some extent due to suppression of gastric acid. But, in this case, this patient took PPI only from the day before ESD and he didn't have any underlying disease. We thought if PPI/H2RA was one of the cause of CMV associated ulcer, so many patient undergone ESD might developed multiple deeper ulcers. Moreover, in this case, CMV ulcer located only one part of the stomach where steroid was locally injected. That's why we think local steroid injection might cause the focal immunosuppressive condition.

COMMENT 4. Did authors check status of cytomegalovirus infection in gastric cancer resected lesion of ESD?

### RESPONSE

In our University, all patients were examined carefully with NBI enhanced magnified esophagogastroduodenoscopy to evaluate background gastric mucosal conditions such as atrophic change, metaplastic change and Helicobacter pylori infection not only the cancer lesion. Of course, we check the other infectious disease. For instance, HBV, HCV, HIV and so on.

COMMENT 5. Patients with ulcerative colitis or Crohn's disease treated with steroid with cytomegalovirus infection were rare to have cytomegalovirus-induced gastric ulcer. How about this discrepancy? Did you check intestine or colon in this case?

### RESPONSE

We agree with you. Patients with ulcerative colitis or Crohn's disease treated with steroid often suffer from CMV ulcer in the colon. We think the long-acting nature of TA which was locally injected into the submucosa may remain highly-concentrated in the artificial ESD ulcer floor for a long time and it induced focal strong immunosuppressive condition of post-ESD ulcer floor which activates CMV activity.

COMMENT 6. No information for treatment of cytomegalovirus infection-induced ulcer.

### RESPONSE

As you pointed out, we didn't mention the reason why ganciclovir was not administered. As the patient wasn't a compromised host and had no other underlying disease, we thought the CMV activity of the ulcer floor was limited and focal. The CMV ulcer was occurred under focal immunosuppressive condition by TA. We considered after TA effect would subside about for 14 days, the CMV activity would decrease and the ulcer healed. But it was necessary for us to follow up the ulcer by frequent endoscopy. Actually we performed follow up endoscopy at POD12, 20 and 30 and confirmed negative conversion of CMV by serology test and histopathological examination.

COMMENT 7. Authors should summarize characteristics of cytomegalovirus-induced

gastric ulcer in Discussion section, irrespective to use of steroid.

RESPONSE

I am sorry that as you pointed out, we didn't mention the summarize characteristics of cytomegalovirus-induced gastric ulcer.

We added some sentences (Page 7, line 6) as follows: CMV is recognized an important pathogen of severe infections in immunocompromised hosts, and causes CMV mononucleosis with multi-organ involvements. In general, CMV- related ulcers might make multiple and deeper lesions in digestive tract in upper gastrointestinal endoscopy.

COMMENT 8. Authors should add appropriate references in Introduction and Discussion sections.

RESPONSE

I am sorry for my careless mistakes with regard to references in Introduction and Discussion sections. We revised and added appropriate references (Page 8, line5-12) (Page 8, line16-20) (Page 9, line20-23).

COMMENT 9. Please add references to reveal evidences of local injection of triamcinolone acetonide after endoscopic submucosal dissection.

RESPONSE

As you pointed out, we didn't add references to reveal evidences of local injection of triamcinolone acetonide after ESD. We added some references (Page 9, line 20).

Minor points:

COMMENT 1. Did you check C7HRP?

RESPONSE

I am sorry we didn't check CMV antigen (C7HRP). We should have checked it. We examined only CMV antibody (IgG, IgM).

Sincerely yours,

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related worsening ulcers after applied steroid cream. But in other fields, there are no report about CMV-associated ulcer development related to the side effects of local steroid injection.

Sincerely yours,

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