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Editor-in-Chief

World Journal of Gastroenterology

Dear Dr. Tarnawski;

Manuscript NO: 45390

Title: Colon perforation due to antigenemia-negative cytomegalovirus
gastroenteritis after liver transplantation: A case report

Thank you for your kind e-mail on February 14, 2019, regarding our
manuscript. According to the reviewers and editorial officer's suggestions, the
manuscript has been carefully revised. The revisions are indicated in red and
are underlined. We hope that our revised paper has been adequately improved
and that it will appeal to the readers of your journal. We would be grateful if
you could kindly reconsider this manuscript for publication in the *World Journal
of Gastroenterology*.

Yours sincerely,

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First of all, as the reviewers and editorial officer's evaluate our manuscript language quality is at level B, we ordered the editing to the professional English language editing company that your editorial office recommended.

Response to Reviewer.

#1 Reviewer's comment: This is a well documented, chronologically presented nice case report. It is about a rare situation related to colon perforation due to antigenemia-negative CMV gastroenteritis after a solid organ (liver) transplantation. Figures are perfect, very informative. Language is fluent. Authors cite 28 appropriate references. Discussion is adequate. Final message emphasizing regular monitoring by endoscopy the symptomatic patient for CMV gastroenteritis even if antigenemia is negative, is clinically important. It is worth publishing by high priority.

Answer: Thank you very much for the comment.

#2 Reviewer's comment: The authors indicated a clinical case of transverse colon perforation due to antigenemia -negative cytomegalovirus (CMV) gastroenteritis, following a living donor liver transplantation. There was interesting case that the disease was progressed even if the CMV assay was negative. Therefore, it would be better if there were paragraphs analyzing the various possibilities that these clinical cases could be occurred.

Answer: Thank you very much for the comment. We analyzed the possibility that these clinical cases could occur as follows and made the corrections that are indicated in red, which are described in the main document:

DISCUSSION

Page 18 line 11 (revised version)

While there have been reports on rare cases in which patients who had CMV gastroenteritis had CMV-AG results that remained negative throughout the disease course after bone marrow transplantation^[13,18,19], there have been no such reports associated with solid-organ transplantation; however, there have been some reports in which the CMV-AG test was

positive when an intestinal perforation was caused by CMV gastroenteritis^[20,21], including a report in which intestinal perforation were caused by CMV gastroenteritis in patients taking immunosuppressants to treat rheumatoid arthritis.

Page 19 line 15 (revised version)

Recently, there was a report showing that CMV infects vascular endothelial cells and causes ulcers and perforation locally in the intestinal mucosa after solid-organ transplantation^[21].

In our case, in addition to the long-term history of oral PSL therapy for autoimmune hepatitis before transplantation, posttransplantation immunosuppression was essential. This may have caused CMV gastroenteritis with strong, localized inflammation that led to intestinal perforation without viremia.

#3 Reviewer's comment:

Comments to the manuscript: Colon perforation due to antigenemia-negative cytomegalovirus gastroenteritis after liver transplantation: Case report.

It is a very interesting clinical case report, by Yokose T., and co-workers, that was related with the treated a case of transverse colon perforation due to antigenemia (AG)-negative cytomegalovirus gastroenteritis, following a living donor liver transplantation.

Title: It is appropriate.

Abstract: It is appropriate.

Background: The introduction is adequate and allows a proper understanding of the problem of study. Although, it is recommended that the authors describe more scientific background related to autoimmune hepatitis. It is also recommended that the authors, explain in more detail, what would be the interpretation of the finding that the serologic tests for CMV showed that the patient was IgG positive (+), IgM negative (-), and AG negative?

Methods and Results.

Was a PCR test for CMV done to the patient before being transplanted?

The researchers could explain with more details the reasons why they use as a donor the patient's second son, even if he was CMV IgG + / IgM-?

There is some protocol to accept CMV IgG + subjects as donors?

Results: It is recommended to describe the following aspects:

1. The sociodemographic, and anthropometrical characteristics of the patient.
Discussion: It is suggested that the authors present at the end of the discussion a list of suggestions to follow in the case of liver transplantation in patients chronically treated with immunosuppressants. In addition, describe the most reliable laboratory tests such as PCR to detect CMV, and the value of IgG / IgM tests, and other aspects of interest to the reader.

Answer: Thank you very much for the comment. We addressed the reviewer's questioned as follows and the corrections are shown in red in the main document:

Reviewer's Comment #3-1: Although, it is recommended that the authors describe more scientific background related to autoimmune hepatitis.

Answer: Thank you very much for the comment. We provided more scientific background related to autoimmune hepatitis in the following paragraph:

INTRODUCTION

Page 8 line 9 (revised version)

Autoimmune hepatitis is an autoimmune disease that commonly develops in middle-aged or older woman and usually causes chronic and progressive liver damage. In regard to treatment, immunosuppressants, especially prednisolone, are commonly used. Liver transplantation is the final therapeutic option for patients, such as in a recently reported case on a patient with autoimmune hepatitis who developed decompensated cirrhosis due to an insufficient response to medical treatment.

Reviewer's Comment #3-2: It is also recommended that the authors, explain in more detail, what would be the interpretation of the finding that the serologic tests for CMV showed that the patient was IgG positive (+), IgM negative (-), and AG negative?

Answer: Thank you very much for the comment. We explain the interpretation of the findings from the serologic tests for CMV as follows:

CASE PRESENTATION

Page 10 line 15 (revised version)

The serologic tests for CMV showed that the patient was IgG positive (+), IgM negative (-), and AG negative, which is indicative of past CMV infection.

Reviewer's Comment #3-3: Was a PCR test for CMV done to the patient before being transplanted?

Answer: Thank you very much for the comment. We described our protocol for the CMV-PCR test as follows:

CASE PRESENTATION

Page 10 line 16 (revised version)

A PCR test for CMV was not performed routinely before transplantation at our facility and was not performed in this case.

Reviewer's Comment #3-4: The researchers could explain with more details the reasons why they use as a donor the patient's second son, even if he was CMV IgG + / IgM-?

Answer: Thank you very much for the comment. Our donor 's serological test for CMV indicated past CMV infection. We explain the interpretation of the findings of the serologic test and the background of donor selection as follows, and the corrections that we made are shown in red in the main document:

CASE PRESENTATION

Page 11 line 7 (revised version)

A blood-type compatible, LDLT was performed using a left lobe graft, with the patient's second son as the donor (20 years old, CMV IgG+/IgM-, which is indicative of past CMV infection).

DISCUSSION

Page 16 line 2 (revised version)

Most Japanese individuals are infected with CMV in early childhoods, and it usually remains latent. Therefore, even if a donor candidate had a past

CMV infection, he or she is not excluded as a donor. When the recipient is seronegative while the donor is seropositive for the CMV antibody, the risk of onset of CMV infection after organ transplantation is high, and appropriate monitoring and prophylactic measures are necessary. However, when the recipient is seropositive, whether the recipient is at risk of infection when the donor is seropositive or seronegative is controversial.

Reviewer's Comment #3-5: There is some protocol to accept CMV IgG + subjects as donors?

Answer: Thank you very much for the comment. Even if the donor was seropositive, we follow the protocol as follows:

CASE PRESENTATION

Page 11 line 14 (revised version)

At our facility, in accordance with the protocol of CMV monitoring and treatment after a liver transplant, CMV-AG is tested twice a week, but a CMV-PCR test is not performed routinely. In addition, prophylactic ganciclovir (GCV) is not administered prophylactically, but is initiated when the patient turns CMV-AG positive. or in the case of a seropositive donor.

Reviewer's Comment #3-6: It is recommended to describe the following aspects:

1. The sociodemographic, and anthropometrical characteristics of the patient.

Answer: Thank you very much for the comment. We have addressed the reviewer's request that we describe the sociodemographic and anthropometrical characteristics of the patient, such as race, occupation, performance status, height, weight, and vital signs. We describe these characteristics as follows and the corrections are shown in red in the main document:

CASE PRESENTATION

Page 9 line 10 (revised version)

The patient was a 52-year-old Asian woman.

Her occupation was a housewife.

According to the Eastern Cooperative Oncology Group Performance Status,

her performance status was 2. At the physical examination, the patient's height was 155 cm, her weight was 47 kg, and her vitals were stable;

Reviewer's Comment #3-7: It is suggested that the authors present at the end of the discussion a list of suggestions to follow in the case of liver transplantation in patients chronically treated with immunosuppressants.

Answer: Thank you very much for the comment. We described the suggestions to follow in the case of liver transplantation in patients who are chronically treated with immunosuppressants as follows:

DISCUSSION

Page 20 line 2 (revised version)

Although CMV infection tends to occur at least 3 weeks after transplantation, patients taking immunosuppressive drugs before transplantation may be affected earlier.

Page 22 line 6 (revised version)

In patients who are chronically treated with immunosuppressants before organ transplantation, endoscopy should be performed according to symptoms at an earlier stage after transplantation.

Reviewer's Comment #3-8: In addition, describe the most reliable laboratory tests such as PCR to detect CMV, and the value of IgG / IgM tests, and other aspects of interest to the reader.

Answer: Thank you very much for the comment. We described the interpretation of the reliability of the laboratory test for CMV as follows:

DISCUSSION

Page 22 line 8 (revised version)

As a reliable test, the CMV-PCR test is reported to be superior to the CMV-AG test, but it is not covered by health insurance providers in Japan.

#4 Reviewer's comment: cmv digestive tract disease is severe and fatal when don to recognized and diagnosed, the case report is so good to remind this disease

after liver transplantation

Answer: Thank you very much for the comment.