

Reviewer #1:

1. The background section has been written simply. It is incomplete and does not cover all of your research ingredients, and also, the importance of your article is not prominent enough. In this section, you must create an explicit view of why you are directed to write this topic.

Response: Thank you for your helpful comment. We revised the background section to provide the importance and meaning of this case report.

"*Clostridioides difficile* colitis (CDI) is one of the most common infections in hospitalized patients, characterized by fever and diarrhea. It usually improves after appropriate antibiotic treatment; if not, comorbidities should be considered. Cytomegalovirus (CMV) colitis is a possible co-existing diagnosis in patients with CDI with poor treatment response. However, compared with immunocompromised patients, CMV colitis in immunocompetent patients is not well studied."

2. Keywords should represent key concepts and should reflect a collective understanding of the topic. For determining the correct and most appropriate keywords, you can use Medical Subject Headings (MeSH) or Google Keyword Planner.

Response: Thank you for your comment. We revised the key words as follows

"Cytomegalovirus; *Clostridioides difficile*; Coinfection; Colitis; Immunocompetent; Case report"

3. The introduction is short, and the constructs and concepts in the introduction section are poorly organized. Include more general and specific background in the manuscript, and use more cohesion and coherence in sentences.

**Response:** We reinforced the introduction section following your recommendation.

"Immunodeficiency is the leading risk factor for invasive CMV diseases<sup>[2]</sup>. Invasive CMV disease

s can occur in immunocompromised patients, including transplant recipients or patients with HIV, by primary infection or reactivation and could have significant morbidity and mortality<sup>[3]</sup>. This mostly affects the gastrointestinal tract, comprising 30% of tissue-invasive CMV diseases in immunocompromised patients<sup>[4]</sup>. Clinical manifestation of CMV colitis in immunocompromised patients varies and depends on the site of involvement which could cause odynophagia, abdominal pain, hematochezia, and fever<sup>[4]</sup>.”

“CMV colitis in immunocompetent patients was previously considered very rare. However, there has been an increasing number of case reports in immunocompetent patients<sup>[5,6]</sup>. The Symptoms of CMV colitis in immunocompetent patients also present odynophagia, abdominal pain, hematochezia, and fever<sup>[5,6]</sup>”

“CDI is usually suspected when hospitalized patients develop diarrhea and fever<sup>[9]</sup>. CMV colitis symptoms are clinically indistinguishable from those of CDI. Therefore, if the immunocompromised status of patients who develop CDI does not improve even with appropriate treatment, accompanying CMV colitis should be considered. However, this may not be considered in immunocompromised patients because cases of co-existing CDI and CMV colitis are rare in immunocompetent patients..”

4. Some bibliographic citations which been used are more than 5 years old and obsolete. The authors must update and arrange the bibliography.

**Response:** Thank you for your comment. We updated and arranged the bibliography except for papers that cited cases of CMV colitis in the discussion. We have added and revised sentences and references as follows

(Lines 155-157)

Chaemsupaphan *et al.* also reported that most immunocompetent patients presented with gastrointestinal bleeding compared to immunocompromised patients<sup>[6]</sup>.

(Lines 167-168)

“Generally, patients with CDI are known to recover after 10~14 days of treatment [13,14]”

References

1. Picarda G, Benedict CA. Cytomegalovirus: Shape-Shifting the Immune System. *The Journal of Immunology* 2018; 200: 3881-3889 [DOI: 10.4049/jimmunol.1800171]
2. Yerushalmy-Feler A, Padlipsky J, Cohen S. Diagnosis and Management of CMV Colitis. *Curr Infect Dis Rep* 2019; 21: 5 [PMID: 30771028 DOI: 10.1007/s11908-019-0664-y]
4. Fakhreddine AY, Frenette CT, Konijeti GG. A Practical Review of Cytomegalovirus in Gastroenterology and Hepatology. *Gastroenterology Research and Practice* 2019; 2019: 6156581 [DOI: 10.1155/2019/6156581]
6. Chaemsupaphan T, Limsrivilai J, Thongdee C, Sudcharoen A, Pongpaibul A, Pausawasdi N, Charatcharoenwittaya P. Patient characteristics, clinical manifestations, prognosis, and factors associated with gastrointestinal cytomegalovirus infection in immunocompetent patients. *BMC Gastroenterol* 2020; 20: 22 [PMID: 32000707 PMCID: PMC6990526 DOI: 10.1186/s12876-020-1174-y]
12. Turner NA, Grambow SC, Woods CW, Fowler VG, Jr., Moehring RW, Anderson DJ, Lewis SS. Epidemiologic Trends in *Clostridioides difficile* Infections in a Regional Community Hospital Network. *JAMA Netw Open* 2019; 2: e1914149 [PMID: 31664443 PMCID: PMC6824221 DOI: 10.1001/jamanetworkopen.2019.14149]
14. Guery B, Galperine T, Barbut F. *Clostridioides difficile*: diagnosis and treatments. *BMJ* 2019; 366: l4609 [PMID: 31431428 DOI: 10.1136/bmj.l4609]

\* Abstract and introduction is really poor-organized, they must be arranged from the scratch

**Response:** Thank you for your comment. We revised the introduction as above #3. Moreover, we rearranged the case summary, conclusion, and core tip in the abstract according to your suggestion as follows

(Lines 14-15)

"*Clostridioides difficile* toxin B PCR on stool samples was positive."

(Lines 17-19)

"Unfortunately, the symptoms worsened again with bloody diarrhea and fever. Therefore, a sig

moidoscopy was performed for evaluation, showing a longitudinal ulcer on the sigmoid colon.”

(Lines 23-24)

“Co-existing CMV colitis should be considered in patients with aggravated CDI on appropriate treatment, even in immunocompetent hosts.”

(Lines 29-35)

“Cytomegalovirus (CMV) colitis is rare in immunocompetent patients, but colitis is the main clinical manifestation. The *Clostridioides difficile* infection (CDI) and CMV colitis symptoms might be indistinguishable clinically. Therefore, it is difficult to consider their co-existence in patients suspected of CDI. If a patient treated with CDI does not show clinical improvement, the possibility of co-existing CMV colitis should be considered as one of the differential diagnoses. Sigmoidoscopy with biopsy is crucial in diagnosing co-existing CMV and CDI colitis.”

Reviewer #2:

1. In diarrhea patient, stool check is routine examination, please provide details in Laboratory examinations

**Response:** Thank you for the helpful comment. We have added the following sentence in laboratory examinations

"Stool culture for Salmonella spp., Shigella spp., Campylobacter spp., and Escherichia coli O-157:H7 was negative. In routine stool examination, there is no helminth or protozoa, and stool white blood cell counts are 1~5 cell/high power field."

2. There were conflict between History of past illness and There is no personal and family history, please correct.

**Response:** We have corrected the sentence in the personal and family history section as follows.

"The patient had no family history."