・病例報告・

Clinical remission from treatment dilemma of CMV colitis with ganciclovir use in a critical ill elderly immunocompetent patient

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INTRODUCTION

Cytomegalovirus (CMV) infects more than half of all adults by 40 years of age. It is estimated that 40~100% of immunocompetent adults worldwide are CMV seropositive, CMV remains in a latency state and allows reactivation in immune insufficiency, such as acquired immunodeficiency syndrome (AIDS), inflammatory bowel disease (IBD), organ transplantation, and active malignancy[1, 2] . CMV diseases in immunocompromised patients invade the broad tropism of the human body, such as the lung, retina, and kidney. The gastrointestinal (GI) tract is one of the most common organs of CMV disease. Manifestations of CMV gastroenterocolitis include dysphagia, abdominal pain, diarrhea, GI bleeding, or serious complications with megacolon and bowel perforation. The endoscopic findings are nonspecific, with mucosal ulceration being the most common [3].

We reported an elderly critically ill patient with multiple comorbidities suffering from CMV colitis who faced the treatment dilemma of severe myelosuppression by ganciclovir and severe intestinal complications of CMV colitis. This case report demonstrated successful clinical management through close monitoring of ganciclovir use and prompt platelet transfusion.We reviewed the literature for strict management approaches, including hematopoietic growth factor use in severe cytopenia. Alternatives for ganciclovir are unavailable, and existing corresponding guidelines have been described only in immunocompromised populations. The purpose of this case report and literature review is to help gastroenterologists promptly manage myelosuppression with ganciclovir and achieve the best outcomes in the management of CMV gastroenterocolitis in immunocompetent patients.

CASE REPORT

An 83-year-old male with comorbidities of hypertension, chronic kidney disease (CKD), chronic heart failure, atrial fibrillation, ischemic stroke post mechanical thrombectomy, and prostate carcinoma post prostatectomy was transferred from another hospital because of sepsis, suspected pulmonary etiology, complicated acute kidney injury on CKD, and deterioration to hypotension and desaturation. He was admitted to the intensive care unit (ICU) after intubation and given vasoactive agents. He was given steroid (actually intravenous use methylprednisolone tapering from 1000 mg daily for approximately 4 weeks, followed by enteral prednisolone tapering from 50 mg daily) and empirical meropenem based on bloody bronchial secretion via bronchoscopy without evidence of mycobacteria infection or malignancy. Anti-glomerular basement membrane antibody was negative as well. However, the patient developed profound hematochezia (onset when steroid use approximately 4 weeks) and required multiple red blood cell transfusions. Colonoscopy found multiple colonic ulcers throughout the colon (Figure1 at back cover), and multiple biopsies confirmed CMV colitis, pathological description of mixed inflammatory cell infiltrate, associated with intranuclear inclusions, which are positive for CMV hematoxylin-eosin staining.

He was treated with intravenous renal dose ganciclovir, but ongoing leucopenia (3,400 cells/μL down to 2,300 cells/μL, which included neutrophils at 2,800 cells/μL down to 1,900 cells/μL) occurred since day 4 ganciclovir therapy-associated preexisting thrombocytopenia (thrombocytopenia onset since approximately 4 weeks prior to hematochezia, if he had a platelet count that decreased gradually, which may be related to CMV infection or reactivation). Platelet (PLT) transfusion was given based on PLT at 16,000 cells/μL (<50,000 cells/μL) with ongoing hematochezia, although renal function improved under intermittent hemodialysis in the ICU. At this moment, we faced the treatment dilemma of continuing or cessation of ganciclovir, which put the patient at risk of either further myelosuppression or severe intestinal complications such as bowel perforation, and life-threatening GI bleeding. Subsequently, the patient was being continued with a lower dose of ganciclovir (maintained a previously adjusted renal dose but did not titrate up the dose, although renal function almost normalized at that moment), given platelet transfusion accordingly associated with close monitoring of the hemogram. Encouragingly, his white blood cell count gradually normalized, and hematochezia ceased after approximately 2 weeks of ganciclovir treatment and succeeded in extubation. The patient was continuing ganciclovir treatment with a suggestion of a 6-week treatment duration. He was discharged from the ICU 3 days after extubation; unfortunately, the patient died of respiratory failure a few days later.

DISCUSSION

There is no consensus on the use of antiviral treatment of CMV gastroenterocolitis in immunocompetent patients. In our index case, the patient was in a relatively immunosuppressive situation after 4 weeks of high-dose steroid use; at that moment, profound hematochezia occurred. In addition, he was advanced in age with multiple comorbidities, particularly chronic kidney disease. Galiatsatos P et al.[4] demonstrated a higher mortality rate in male patients over the age of 55 and in chronic diseases such as diabetes or chronic kidney disease in a meta-analysis of CMV colitis in immunocompetent hosts, whereas previous healthy young patients had an excellent prognosis without any intervention.

Myelosuppression is the most serious and common adverse reaction to ganciclovir. Among myelosuppression cases, neutropenia

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and anemia are very common (>=10%), whereas leucopenia, thrombocytopenia and pancytopenia are common (>=1%, <10%).[5] Ganciclovir should be used with caution in patients with preexisting or drug-related hematological cytopenia and in patients receiving radiotherapy.

Therapy should not be initiated if the absolute neutrophil count is < 500 cells/μL or the PLT count is < 25,000 cells/μL (our case 16,000 cells/μL before ganciclovir was started, but that was corrected after PLT transfusion) or the hemoglobin is < 8 g/dL (our case 9.1 g/dL when ganciclovir was initiated). Neutropenia usually occurs during the first or second week of therapy. The cell count usually normalizes within 2 to 5 days after discontinuation of the drug or dose reduction[5].

It is recommended to monitor complete blood counts during therapy[5], particularly in patients with renal impairment. During the first 2 weeks, a white blood cell count is recommended every second day; if there are low baseline neutrophil levels (< 1000 neutrophils/μl) or leucopenia during previous therapy with other myelotoxic substances and those with renal impairment, monitoring should be performed daily.

Hematopoietic growth factors and/or the interruption of ganciclovir therapy is indicated in patients with severe leucopenia, neutropenia, anemia and/or thrombocytopenia. Hematopoietic growth factors (e.g., granulocyte-colony stimulating factor, G-CSF or granulocyte macrophage colony-stimulating factor, GM-CSF)[6] are particularly useful when ongoing anti-CMV treatment is necessary and has the disadvantage of switching to other alternatives.

Foscarnet, Cidofovir and Letermovir are FDA-approved alternatives for ganciclovir/prodrug valganciclovir contraindicated individuals[7]; however, these alternatives are not universally available, including in our hospital.

The efficacy and toxicities of antiviral agents for CMV disease in immunocompetent hosts remain unproven since the majority of these patients recover without intervention. Instead, that were evaluated extensively only in immunocompromised patients[8].

The therapeutic dosage and duration of ganciclovir for treating CMV colitis in immunocompetent individuals could refer to current guidelines[9, 10] ECCO 2014 and HHS 2020, summarized as below (Table 1).

Table 1. Guidelines for CMV colitis as per ECCO 2014 and HHS 2020.

Guideline for CMV colitis	ECCO 2014 (European Crohn's and Colitis Organization)	HHS 2020 (U.S. Department of Health and Human Services.)
Ganciclovir (standard dose)	5 mg/kg iv twice daily	5 mg/kg iv twice daily
Valganciclovir	900 mg po twice daily, after 3 – 5 days of iv ganciclovir	900 mg po q12 h, once oral therapy is tolerated
Total duration of therapy	2 – 3 weeks	21 to 42 days or until symptom resolution
Indication for population	CMV colitis in IBD	CMV colitis in HIV/AIDS

CONCLUSION

Anti-viral treatment for elderly male immunocompetent patients, especially those with comorbidities, has been verified by recent evidence. Myelosuppression is a common side effect of ganciclovir for treating CMV disease, and the clinical dilemma of either the risk of severe myelosuppression by ganciclovir use or severe intestinal complications by CMV colitis is challenging for clinicians, especially when drug alternatives are not available. Therefore, close monitoring and hematopoietic growth factor application in severe cytopenia are crucial. In addition, clinical guidelines for CMV colitis in immunocompetent populations are lacking, and the therapeutic strategy for this population could only refer to existing corresponding guidelines in immunocompromised populations.

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（本文編輯：彭洪泉）

第 64 頁 圖示

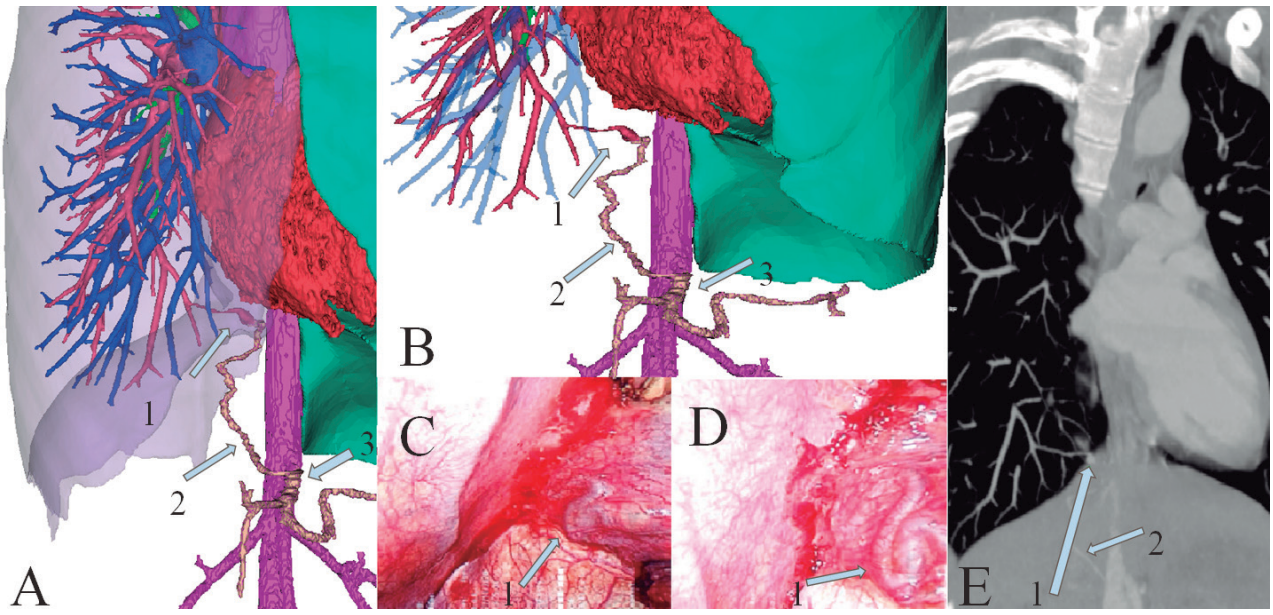

圖1.A,B為CT三維重建示意圖，C,D為術中情況，E為CT圖片。
其中1為瘺管匯合膨隆位置，2為腹腔幹動脈迷走的膈下肌動脈，3為腹腔幹動脈。影像學的血管情況與手術中所見的瘺管情況相符。

第 66 頁 圖示

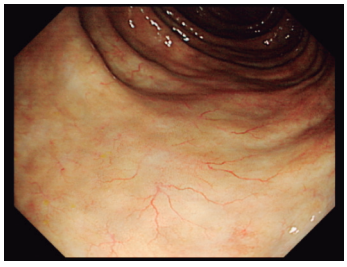

圖1.結腸鏡圖像可見粘膜呈淡藍色改變

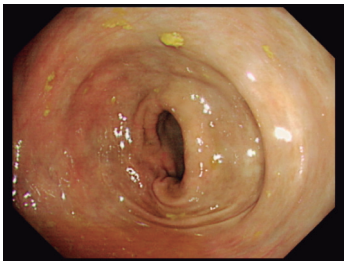

圖2.結腸鏡圖像可見粘膜呈淡藍色改變

第 67 頁 圖示

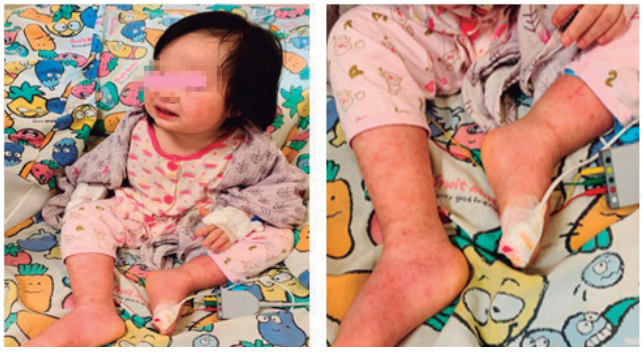

Figure1. Conjunctivitis, red and cracked lips, extremity edema, and petechiae on lower limbs (Day6).

第 70 頁 圖示

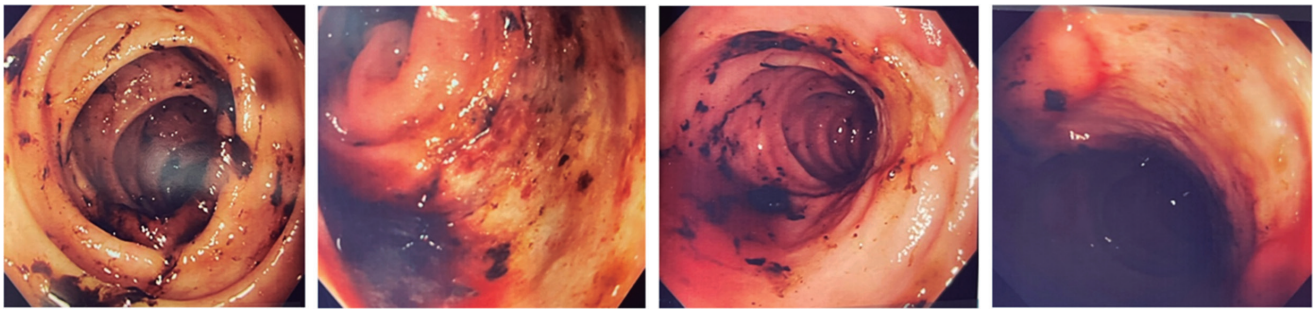

Figure1. Multiple colonic deep ulcerations throughout the colon from the ascending colon to the sigmoid colon.