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POTENTIAL ROLE OF UPADACITINIB IN CYTOMEGALOVIRUS COLITIS RECURRENCE

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ABSTRACT

Background: Cytomegalovirus (CMV) colitis is a common complication in patients with ulcerative colitis (UC), which is often associated with immunosuppressive therapies including steroids, azathioprine, and biologics such as infliximab. Although CMV infections related to upadacitinib, a Janus kinase (JAK) inhibitor, have been reported, they typically occur after prolonged use. Consequently, early onset CMV colitis following the initiation of JAK inhibitors has not been extensively recognised.

Case report: We present the case of a 68-year-old Japanese woman with refractory UC who developed CMV colitis that initially improved but worsened shortly after starting upadacitinib. The patient improved following upadacitinib discontinuation and CMV-specific treatment. This case suggests that early onset CMV colitis after upadacitinib initiation is clinically significant and highlights the importance of monitoring lymphocyte counts and CMV antigen levels during JAK inhibitor therapy.

Conclusion: These findings provide valuable insights into the early risk of CMV reactivation and may guide future management strategies for patients with UC undergoing JAK inhibitor treatment.

KEYWORDS

Cytomegalovirus colitis, upadacitinib, JAK inhibitors, ulcerative colitis

LEARNING POINTS

- This case provides insights into managing cytomegalovirus (CMV)–related adverse effects in patients receiving Janus kinase (JAK) inhibitors.
- The risk of CMV disease, including CMV colitis, should be considered owing to lymphocyte reduction during upadacitinib treatment.

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INTRODUCTION

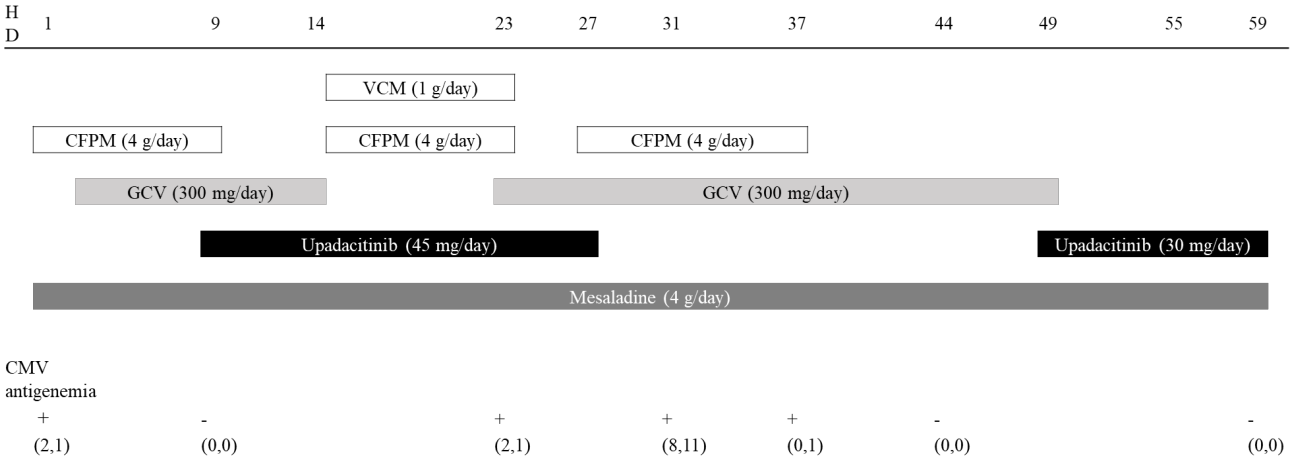
Cytomegalovirus (CMV) colitis is a deoxyribonucleic acid (DNA) virus from the herpesvirus family. Most individuals acquire CMV during childhood, after which the virus remains latent. Although CMV infection is typically asymptomatic in healthy individuals, CMV colitis should be suspected in immunocompromised patients or organ transplant recipients presenting with symptoms such as fever, severe diarrhoea, and bloody stools. The mortality rate for CMV colitis is reportedly 56.9% in immunocompetent men aged >55 years, and 75.2% in immunosuppressed patients, indicating a highly unfavourable prognosis[1]. Additionally, in patients with inflammatory bowel disease (IBD), CMV is associated with an increased mortality rate[2].

Upadacitinib, a Janus kinase (JAK) inhibitor, is used to treat moderate to severe ulcerative colitis (UC) and is considered an important agent for maintaining remission. Known adverse events include rash, anaemia, and increased liver enzymes. Additionally, warnings have been issued regarding serious infections, including upper respiratory tract infections, herpes simplex virus, and herpes zoster[3]. However, few reports have addressed CMV infection, and details regarding its timing and mechanism of occurrence remain unclear.

We report a case of CMV colitis that developed during UC treatment and recurred during upadacitinib therapy to highlight considerations for patients on JAK inhibitors.

CASE DESCRIPTION

The clinical course and laboratory findings are presented below *(Fig.1, Table 1)*. A 68-year-old Japanese woman visited our hospital with suspected acute pneumonia. Blood and sputum cultures were obtained and cefepime was initiated at a dose of 2 g every 12 hours. The patient was also being treated for refractory UC with infliximab, azathioprine, and mesalazine. On hospital day 1, she presented with fatigue, >20 episodes of diarrhoea per day, abdominal pain, and dyspnoea. On day 2, endoscopic examination revealed extensive map-like ulcers in the sigmoid colon. Given the worsening UC, infliximab and azathioprine were discontinued. Conversely, immunohistochemical staining of the colon biopsy revealed the presence of CMV-positive cells *(Fig. 2A and C)*, and a CMV antigenemia assay (C10/C11 method) yielded a positive result (2/1: leucocyte count 50,000). Therefore, treatment with 150 mg of ganciclovir every 12 hour was initiated for CMV colitis. Stool cultures ruled out *Clostridium difficile*. By day 9, respiratory status improved (SpO2 99% on room air) and cefepime was discontinued; upadacitinib (45 mg/day) was initiated for the UC. Additionally, a repeat CMV antigenemia test was conducted and was negative on HD14 (0/0: leukocyte count, 50,000). Since the frequency of diarrhoea had decreased to 7 times per day and abdominal symptoms improved, ganciclovir was discontinued after 2 weeks of administration. On day 15, a body temperature of 37.8°C was observed, raising the suspicion of bacterial infection. Blood cultures were then obtained, and treatment with cefepime and vancomycin was initiated. On day 23, blood cultures were negative, leading to cefepime and vancomycin discontinuation. However, a CMV antigenemia test returned positive (2/1: leukocyte count 50,000) and the frequency of diarrhoea increased to 17 times per day; thus, ganciclovir was resumed. On day 27, the patient had a fever of 37.6°C. Although UC had remained in remission since upadacitinib initiation, concerns regarding reactivation of CMV colitis due to its immunosuppressive effects led to the decision to temporarily discontinue its use. Additionally, owing to the suspicion of pneumonia recurrence, cefepime was resumed. Tests for the influenza virus and severe acute respiratory syndrome coronavirus 2 were negative. On day 31, lymphopenia was confirmed, and the CMV antigenemia test showed an increase in positive cells (8/11: leukocyte count 50,000). A colonoscopy revealed extensive map-like ulcers in the sigmoid colon and haemorrhagic mucosa. Immunohistochemical staining of colon biopsy specimens confirmed the presence of CMV-positive cells *(Fig. 2B and D)*. Therefore, it was determined that the recurrence of CMV enteritis was attributable to upadacitinib, and a decision was made to withhold its use while monitoring the patient's



Abbreviation: HD, hospital day; VCM, vancomycin; CFPM, cefepime; GCV, ganciclovir; CMV, cytomegalovirus. Number of CMV antigen–positive cells in 50,000 leukocytes

Figure 1. Clinical course of this case.

	Day 1	Day 9	Day 14	Day 23	Day 27	Day 31	Day 37	Day 49	Day 55	Day 59
White blood cell (cells/µl)	2800	3600	4200	4600	5100	3600	3900	3400	6400	4800
Neutrophil (cells/µl)	1450	1930	2140	3080	3180	2760	2490	1550	3290	-
Lymphocyte (cells/µl)	1070	1530	2010	1060	1410	630	1190	1600	2460	-
Monocyte (cells/µl)	180	60	70	20	30	20	40	50	40	-
Eosinophil (cells/µl)	10	10	0	20	30	20	40	50	40	-
Basophil (cells/µl)	0	0	20	10	10	0	10	30	40	-
Haemoglobin (g/dl)	8.4	8	6.8	9	8.6	8.9	9.4	8.9	10.3	8.1
Platelet ($\times 10^3$/µl)	462	301	389	537	676	617	397	328	730	728
Albumin (g/dl)	1.3	-	-	1.5	1.6	1.7	1.8	1.8	2.3	2.5
AST (IU/l)	9	14	49	15	14	11	11	13	18	16
ALT (IU/l)	3	7	49	16	17	10	8	11	15	11
Creatinine (mg/dl)	0.48	0.32	0.33	0.32	0.31	0.38	0.36	0.37	0.49	0.51
CRP (mg/dl)	10.93	0.63	0.77	0.54	1.39	1.6	0.23	0.59	0.51	0.26

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein.

Table 1. Laboratory values.

progress. On day 37, blood cultures returned negative, leading to the discontinuation of cefepime. Furthermore, a CMV antigenemia test showed a decrease in the number of positive cells (0/1: leukocyte count, 50,000). On day 44, the CMV antigenemia test returned negative (0/0: leukocyte count 50,000), and the frequency of diarrhoea decreased to 5 times per day. Immunohistochemical staining of day 49 colon biopsies did not reveal CMV-positive cells, and ganciclovir treatment was discontinued. Upadacitinib was resumed at a reduced dose of 30 mg/day. The patient was transferred to another hospital on day 55. During an outpatient visit on day 59, the CMV antigenemia test remained negative (0/0: leukocyte count, 50,000) and there was no evidence of recurrence. The patient's condition remained stable.

DISCUSSION

In our case, CMV colitis recurred shortly after the initiation of upadacitinib, following the improvement of CMV colitis

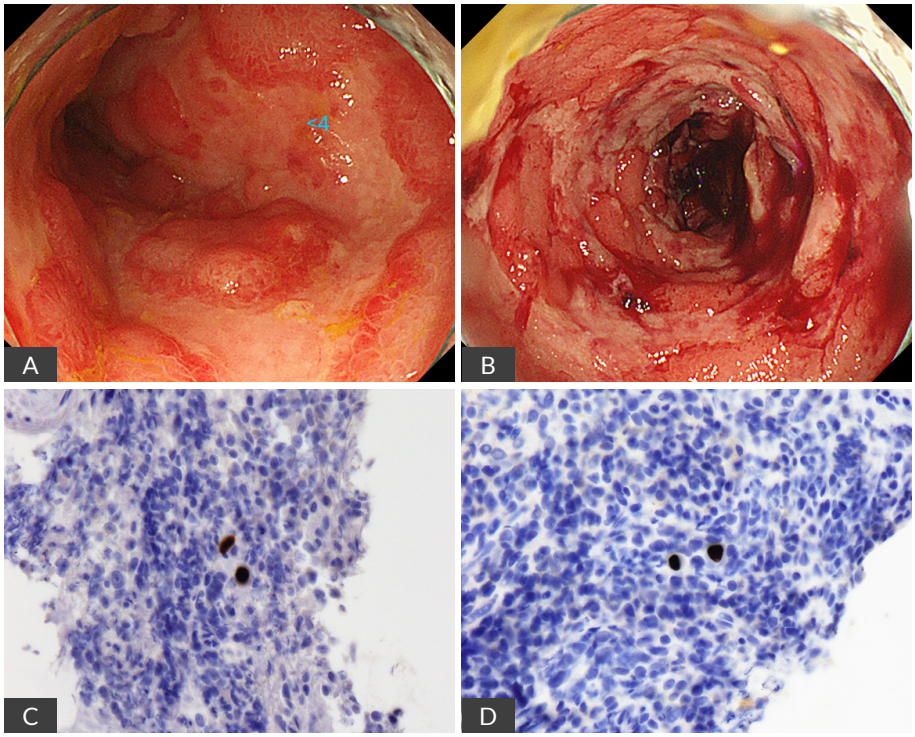


Figure 2. Endoscopic findings and positive immunohistochemistry (IHC) staining for cytomegalovirus (CMV) in colon biopsies. A) First colonoscopy (on day 2) reveals extensive map-like ulcers in the sigmoid colon; B) Time of recurrence (day 31): extensive map ulceration of the sigmoid colon worsened, and the mucosa was prone to bleeding.; C-D) Positive IHC staining for CMV in colon biopsies on hospital days 2 (C) and 31 (D). Bar: 20 µm.

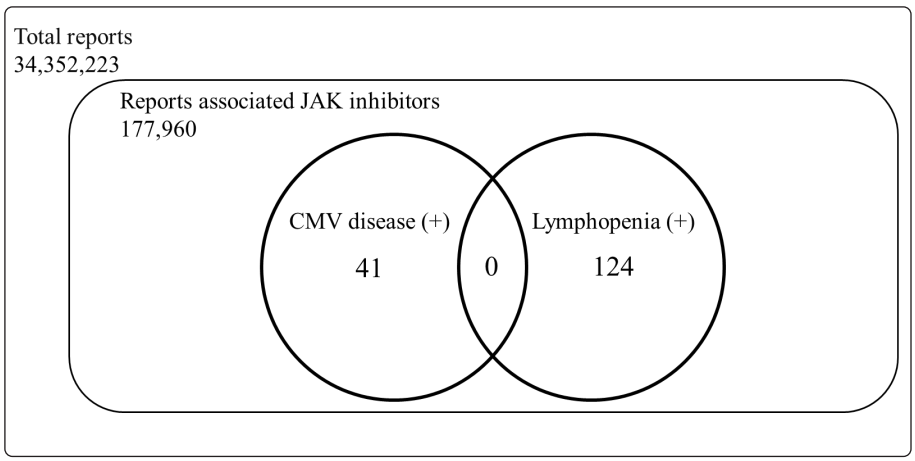


Figure 3. Reports on cytomegalovirus (CMV) disease and lymphopenia associated with Janus kinase (JAK) inhibitors using VigiBase in the literature. There were 41 reports on CMV disease associated with JAK inhibitors, and there were 124 reports on lymphocytopenia. However, no study has documented both conditions simultaneously. The JAK inhibitors include tofacitinib citrate, baricitinib, upadacitinib, filgotinib maleate, and itacitinib.

in a patient with UC. CMV colitis reportedly occurred 9 months after upadacitinib initiation[4]. However, in our case, CMV colitis developed 2 weeks after treatment initiation, representing the first reported case of an exacerbation of CMV following short-term upadacitinib administration.

CMV is associated with lymphopenia. Patients with systemic lupus erythematosus and CMV have a lymphocyte count of 680/μl, significantly lower than that of asymptomatic patients (1,520/μl)[5]. In this case, the lymphocyte count decreased to 630/μl during CMV colitis recurrence, suggesting that lymphocyte depletion may have contributed to the onset of CMV colitis. Additionally, considering the reported side effects of lymphopenia associated with upadacitinib[6], a relationship with upadacitinib administration was also presumed. However, the onset of lymphopenia with this drug reportedly occurs approximately 60 weeks after treatment initiation. In patients taking upadacitinib, a temporary increase in lymphocyte count has been observed a few months following therapy initiation, followed by a return to baseline after 40 weeks[7]. This phenomenon is also observed with another JAK inhibitor, tofacitinib[8]; thus, the lymphopenia that occurred after 2 weeks of upadacitinib administration in this case seems unlikely. However, it has been reported that lymphopenia with upadacitinib occurs dose-dependently[6]. Upadacitinib is typically initiated at an induction therapy dose of 45 mg/day, and lymphopenia occurs thereafter. However, when upadacitinib was restarted at a reduced dose of 30 mg/day after improvement in CMV and lymphopenia, no further lymphopenia was observed, suggesting a possible association between high dose upadacitinib administration and lymphopenia. Therefore, it cannot be denied that lymphopenia due to high dose upadacitinib administration may have contributed to the development of CMV colitis in this case.

In previous reports of cases associating CMV colitis with upadacitinib, lymphopenia was not observed[4]. On the other hand, JAK has been associated with the onset of CMV infection. CMV-infected cells can evade immune responses involving interferon alpha (IFN-α) and interferon gamma by inhibiting the JAK/STAT pathway. Reports have shown that upadacitinib and tofacitinib significantly inhibit JAK1/TYK2 in IFNα/pSTAT5 compared to filgotinib[9]. Thus, it cannot be denied that upadacitinib itself may carry a risk of causing CMV disease. Therefore, we analysed signals for the occurrence of CMV disease associated with JAK inhibitors using VigiBase, an adverse event reporting database supervised by the World Health Organization. A significant disproportionality was observed between CMV disease and JAK inhibitors including upadacitinib, tofacitinib, etc., suggesting a potential association between JAK inhibitors and CMV disease *(Table 2)*. Additionally, among the patients who reported CMV disease while using JAK inhibitors, there were no reports of lymphopenia *(Fig. 3)*, indicating that CMV may be an independent adverse effect in patients treated with JAK inhibitors. Therefore, JAK inhibition may be involved in the development of CMV disease.

In this case, secondary CMV colitis developed initially following UC. Although CMV colitis recurrence due to worsening UC was considered, it was ruled out as UC showed a trend of improvement with upadacitinib administration. The patient was not on other immunosuppressive medications, and lymphocyte depletion was ruled out as IFX and AZA had been discontinued. Although the patient continued mesalazine, no reports link mesalazine to lymphocyte depletion, and the patient had been taking it before admission, making it an unlikely cause.

One limitation of this case is that CMV colitis improvement was initially assessed only by CMV antigenemia testing,

AE	AE without JAK inhibitors/total (%)	AE with JAK inhibitors/total (%)	ROR (95% CI)
Cytomegalovirus disease	2735/34,174,263 (0.0080%)	41/177,960 (0.023%)	2.88 (2.06-3.92)

Abbreviation: AE, adverse event; ROR, reporting odds ratio; CI, confidential intervals.
*JAK inhibitors: tofacitinib citrate, baricitinib, upadacitinib, filgotinib maleate, and itacitinib.

Table 2. Increased risk of developing cytomegalovirus disease with Janus kinase (JAK) inhibitors in VigiBase.*

without immunohistochemical staining of colonic biopsies. Therefore, although the CMV antigenemia test has high sensitivity and specificity, it is insufficient for diagnosis on its own, and the possibility of incomplete CMV colitis resolution cannot be ruled out. In this case, CMV-positive cells increased significantly during CMV colitis recurrence, despite no worsening of UC symptoms, suggesting the possibility of recurrence. Additionally, the standard 2-week treatment for CMV colitis involves administering ganciclovir, the first-line therapy for CMV. In patients with CMV colitis and IBD, intravenous ganciclovir for 2 weeks has shown better outcomes than 1-week intravenous or 2-week oral treatments[10]. Therefore, the 2-week intravenous ganciclovir administered in this case was considered adequate for effective CMV colitis management. This case provides insights into managing CMV-related adverse effects in patients receiving JAK inhibitors.

Overall, it is essential to consider the risk of CMV disease, including CMV colitis, owing to lymphocyte reduction during upadacitinib treatment. Dose reduction should be considered in elderly patients, and proactive testing is necessary when symptoms arise, as CMV disease can develop early after initiating upadacitinib therapy.

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