JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Case Report

Cytomegalovirus and Epstein-Barr Virus reactivation in steroid-refractory immune checkpoint inhibitor colitis

Joyce Sanyour[1 #], Bassem Awada[2 #], Ahmad Mattar[3], Rasha Matar[1], Nausheen Yaqoub[4], Ibrahim Al Haddabi[5], Khalid Al-Baimani[3], Issa Qarshoubi[1]

[1] Gastroenterology Division, Internal Medicine Department, Sultan Qaboos Comprehensive Cancer and Research Center (SQCCCRC), University Medical City (UMC), Muscat, Sultanate of Oman
[2] Infectious Diseases Division, Internal Medicine Department, Sultan Qaboos Comprehensive Cancer and Research Center (SQCCCRC), University Medical City (UMC), Muscat, Sultanate of Oman
[3] Medical Oncology Department, Sultan Qaboos Comprehensive Cancer and Research Center (SQCCCRC), University Medical City (UMC), Muscat, Sultanate of Oman
[4] Histopathology Department, Sultan Qaboos Comprehensive Cancer and Research Center (SQCCCRC), University Medical City (UMC), Muscat, Sultanate of Oman
[5] Laboratory Medicine, Sultan Qaboos Comprehensive Cancer and Research Center (SQCCCRC), University Medical City (UMC), Muscat, Sultanate of Oman

# Authors contributed equally to this work.

Abstract

Introduction: Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) reactivation are known complications in immunocompromised hosts, particularly transplant recipients. However, their occurrence and clinical implications in patients with solid tumors remain underexplored. The introduction of immune checkpoint inhibitors (ICIs) has transformed cancer therapy, but immune-related adverse events (irAEs), including colitis, are increasingly recognized. The potential role of viral reactivation in exacerbating these toxicities is not well established.

Cases Presentation: We report two cases of patients with solid tumors treated with ICIs who developed severe, refractory immune-related colitis. Extensive evaluation revealed markedly elevated CMV and EBV viral loads in colonic biopsies, confirmed by histopathology. Both patients showed significant clinical and endoscopic improvement following antiviral therapy with ganciclovir, highlighting the role of CMV and EBV in modulating the severity of ICI-induced colitis.

Conclusions: CMV and EBV reactivation may contribute to the persistence or worsening of ICI-induced colitis. Early recognition and treatment of viral reactivation in patients with irAEs may improve outcomes. Clinical judgment and serial viral monitoring are essential for guiding management decisions.

Key words: Cytomegalovirus; immune-checkpoint inhibitors; immune-related adverse events; immune-related colitis.

J Infect Dev Ctries 2025; 19(8):1276-1282. doi:10.3855/jidc.21109

(Received 26 November 2024 – Accepted 12 March 2025)

Introduction

Immune checkpoint inhibitors (ICIs) such as ipilimumab, nivolumab, and pembrolizumab are highly effective drugs that target specific molecules in immune and cancer cells, including T lymphocytes and tumor cells [1]. These drugs work by blocking these molecules, which in turn boosts the immune system's response against cancer cells [1]. ICIs have been approved for several types of cancer, including triple-negative breast cancer (Estrogen receptor-negative, progesterone receptor-negative, HER-2 negative), which is the most aggressive type of breast cancer [2]. In such cases, there are no targeted or hormonal therapy. ICIs have been shown to be effective in both neoadjuvant and metastatic settings when PD-L1 $\geq$ 10% [2,3]. The Keynote-522 trial demonstrated that pembrolizumab, in combination with chemotherapy in the neoadjuvant setting, resulted in a 14.3% higher pathologic complete response compared to chemotherapy alone [3]. Additionally, there was a 5% improvement in 5-year overall survival [3].

While they have been approved to treat various types of cancers, they can also cause adverse effects on different organs, including the colon, leading to colitis [1]. The treatment of immune-related colitis (IMC) is mainly withholding the ICI plus steroid therapy. Despite steroid therapy, patients may present with refractory colitis where infliximab may be considered

after ruling out other differentials, including infectious pathogens [4].

Cytomegalovirus (CMV) and *Epstein-Barr virus* (EBV) are two viruses that belong to the *Herpesvirus* family [5,6]. In immune-competent patients, primary CMV or EBV infections are self-limited infections. However, once the immune system weakens, CMV or EBV can reactivate, causing life-threatening conditions. EBV reactivation can lead to fatal lymphoproliferative disorders, including post-transplant lymphoproliferative disorder (PTLD), hemophagocytic lymphohistiocytosis (HLH), or EBV mucosal ulcerations (EBVMU), while CMV reactivation can lead to life-threatening tissue invasive diseases like pneumonitis, colitis, hepatitis, and nephritis [5,6]. The reactivation of EBV and CMV is well-known in transplant patients; however, it's rarely studied in other immunocompromised patients [7]. Herein, we report two cases of steroid refractory immune-related colitis post-ICI. In both cases, the persistence of immune-related colitis was associated with CMV and EBV reactivation in the colonic tissue.

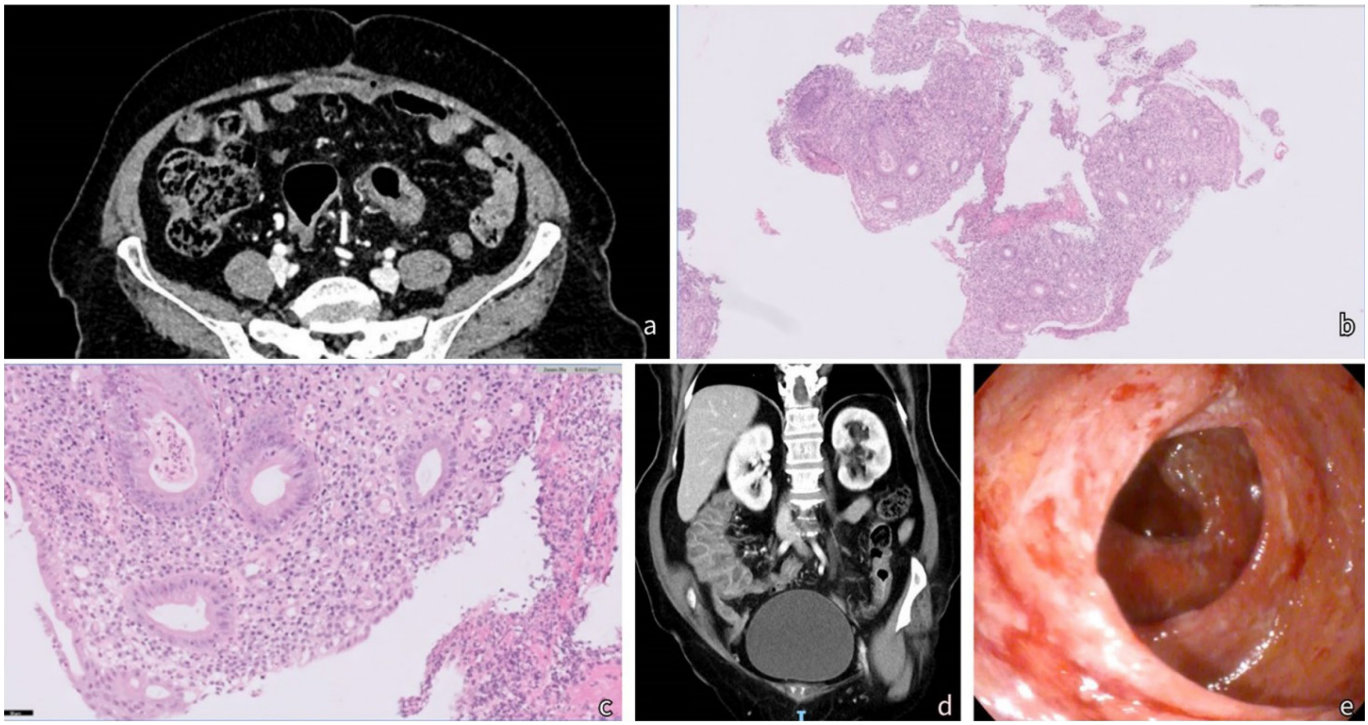
Cases Presentation

Case 1

A 62-year-old female patient with a history of diabetes mellitus, hypertension, and triple-negative left-sided breast cancer on neoadjuvant chemotherapy: Adriamycin plus Cyclophosphamide and Pembrolizumab. On the 16th of March, after seven cycles of Pembrolizumab, she presented with grade II diarrhea plus abdominal pain of five days duration. There was no rectorrhagia, fever, or chills. The vital signs were within normal. Her physical examination was unremarkable, with a soft, non-tender abdomen.

On admission, the white cell count was 4200 cells/mm^3 with a neutrophil count of 59% and a lymphocyte count of 22%. Her C-reactive protein (CRP) level was 11 mg/L. The liver function tests (LFTs), creatinine levels, and electrolytes were normal. In addition to that, blood and stool cultures were sent. She was started empirically on IV piperacillin-tazobactam 4.5 g every 8 hours after a negative *Clostridium difficile* screening test. A Computed tomography (CT) scan abdomen-pelvis showed a diffuse wall thickening involving a segment of sigmoid colon and adjacent descending colon, likely inflammatory in nature (Figure 1a). For that, antibiotics

Figure 1. Radiological, histopathological and macroscopic colonic tissue showing severe colitis.



a) CT scan abdomen-pelvis showing diffuse wall thickening of the descending colon. **b)** Colonic mucosa with surface erosions and dense lymphoplasmacytic infiltrate in lamina propria. (H & E 5 x). **c)** High power magnification of colonic biopsy highlighting dense chronic inflammation with cryptitis and crypt abscess formation (H & E 20 x). **d)** Interval development of significant circumferential mural thickening involving the cecum and ascending colon. **e)** Diffuse erythematous mucosa with deep ulcerations in the ascending colon.

were stopped, and she was started on methylprednisolone 2 mg/kg Intravenously (IV). On day two of admission, she underwent a colonoscopy that revealed diffuse mucosal inflammation and hyperaemia with scattered erosions (Figure 1b). The histopathological evaluation showed diffuse moderate acute and chronic inflammation with cryptitis and crypt abscess formation (Figure 1c). CMV was negative in both blood and colonic tissue. The patient improved clinically on steroids, and for that, she was discharged on a prednisone tapered dose.

A week later, she was re-admitted for worsening her diarrheal illness, reaching eight episodes per day of bloody diarrhea with diffuse abdominal pain. A repeat stool culture and C. diff studies were negative. The CT scan abdomen-pelvis revealed significant circumferential mural thickening in the cecum and ascending colon in keeping with colitis, plus an increase in the proctosigmoiditis extending into the distal descending colon (Figure 1d). A colonoscopy was performed, and it showed severe procto-colitis involving the recto-sigmoid, ascending colon, and caecum with deep ulcerations. Infliximab 5gm/kg IV was started at 0, 2, and 6 weeks. The histopathology result showed severe chronic colitis with ulceration. The CMV and EBV PCR turned positive with 61,921 IU/mL for CMV and 138.261 IU/mL for EBV. No CMV-like inclusions were seen. Taking into consideration the severity of the illness and the high viral load, we started valganciclovir 900 mg every 12 hours orally for three weeks. The patient improved clinically with the resolution of the symptoms of diarrhea and abdominal pain.

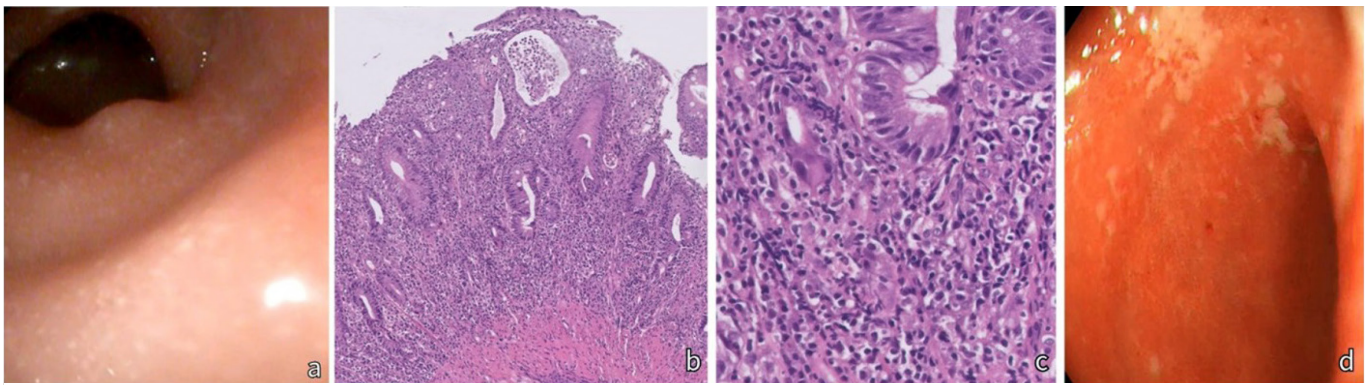
Case 2

A 55-year-old female with left breast cancer was admitted in April 2023 for profuse diarrhea of 6-8 episodes per day and colicky abdominal pain of two months duration. Her history of malignancy goes back to July 2022 when she was diagnosed. She received neoadjuvant chemotherapy (Keynote 522) till December 2022 followed by a left-sided modified radical mastectomy in January 2023. After surgery, she received radiotherapy and was started on Pembrolizumab in February 2023. A month later she started complaining of profuse bloody diarrhea with colicky abdominal pain.

Laboratory testing revealed a normal white cell count. The C-RP level was 5 mg/L. Stool analysis, culture, and C. diff studies all turned negative. The patient underwent a colonoscopy that showed mild to moderate colonic inflammation extending from the rectum to the hepatic flexure (Figure 2a). Tissue for histopathology was sent and it revealed mild ulceration & architectural distortion, and moderate acute and chronic inflammation (cryptitis and crypt abscess). In addition to that, the colonic CMV PCR turned out positive with low titers of 1884 IU/mL and EBV titers of 13,671 IU/mL. The blood CMV and EBV PCR were taken and were negative.

The patient was started empirically on prednisone 2 mg/kg IV and improved dramatically. For that, she was discharged on oral prednisone therapy of 2 mg/kg/day with tapering by 10 to 20 mg every five days. On May 2023, she presented again with profuse diarrhea and colicky abdominal pain. Her vitals were normal. Laboratory testing showed a white cell count of 3770 cells/mm^3 with 58% neutrophils and 27% lymphocytes. A C. diff test and stool culture were negative. A repeated sigmoidoscopy was done and showed a continuous moderate inflammation with superficial ulcerations (Figure 2d). The histopathology showed

Figure 2. Histopathological and macroscopic findings of colitis with positive.



a) mild erythematous mucosa with some aphtous lesions. **b)** Section showing colonic mucosa with surface ulceration, moderate chronic inflammation and crypt abscess formation (H&E 10 x). **c)** Higher magnification showing large nuclei probably representing CMV inclusions. (H&E 40 x). **d)** Diffuse erythematous mucosa with some superficial ulcerations.

chronic inflammation with micro abscesses and megaloblastic features in keeping with CMV proctitis (Figure 2c). The CMV and EBV DNA levels turned positive with 502,683 IU/mL for CMV and 2,425,556 IU/mL for EBV. The patient was started on oral valganciclovir 900 mg every 12 hours for 21 days. The patient's diarrhea resolved after a week of starting antiviral therapy.

Discussion

Herein, we reported two cases of steroid refractory ICI-related colitis who were found to have EBV and CMV colonic reactivation. The diagnosis was made through endoscopic evaluation plus molecular and immune histochemistry testing. Both patients were treated through withholding the ICI, immunomodulator therapy (steroids or infliximab), and oral valganciclovir for CMV disease.

Immune-mediated colitis (IMC) is a common complication that can arise in patients receiving immune checkpoint inhibitors (ICIs). The incidence of IMC varies depending on several factors, including the

Table 1. Published cases of CMV colitis in Patients with Immune Checkpoint Inhibitors related colitis.

Author	Age/Sex	Malignancy	Immune checkpoint inhibitor	Clinical presentation	Colonoscopy findings	Diagnosis	Treatment	Outcomes
Tay et. al. [10]	78 / F	Colo-rectal cancer	NA	NA	Colitis	NA	Ganciclovir IV	Passed away
Tay et. al. [10]	60 / M	Metastatic melanoma	NA	NA	Colitis	NA	Ganciclovir IV	Passed away
Tay et. al. [10]	64 / M	Metastatic melanoma	NA	NA	Colitis	NA	Ganciclovir IV	Passed away
Franklin *et al.* [11]	67/F	Melanoma	Ipilumumab	Refractory diarrhea + hematochezia	NA	CMV DNA on colonic tissue	Ganciclovir IV	Passed away
Franklin *et al.* [11]	77/ M	Melanoma	Ipilumumab	Refractory diarrhea + hematochezia	NA	Positive CMV stain + CMV PCR on colonic tissue	Ganciclovir IV	Resolved
Franklin *et al.* [11]	57/ M	Melanoma	Ipilumumab	Refractory diarrhea + hematochezia	NA	Positive CMV stain + CMV PCR on colonic tissue	Ganciclovir IV	Resolved
Franklin *et al.* [11]	73 / M	Melanoma	Ipilimumab and nivolumab	Refractory diarrhea + hematochezia	NA	CMV DNA on colonic tissue	Ganciclovir IV	Passed away
Katharina Lankes *et al.* [13]	32/ M	Melanoma	Ipilumumab / Nivolumab	Hemorrhagic diarrhea	Crypt abscesses + erosive lesions	Positive CMV stain + CMV PCR on colonic tissue	Ganciclovir IV / Oral valganciclovir	Resolved
Harris et al [14]	66/ M	Melanoma of the scalp	Nivolumab	Refractory watery non-bloody diarrhea	Mild erythema + punctuate ulcerations + Owl's body findings	Colonoscopy findings + CMV PCR (631 IU/ml) on colonic tissue	Valganciclovir	Resolved
Gueguen J *et al.* [15]	70/ M	Melanoma	Pembrolizumab	Severe watery diarrhea + electrolyte imbalance	Pancolitis	Positive CMV stain on IHC	Ganciclovir IV then oral valganciclovir	Resolved but relapse after resumption of the immune checkpoint inhibitor.
van Turenhout *et al.* [16]	73 /F	Melanoma	Ipilimumab / Nivolumab	Diarrhea with hematochezia	Erosive and friable inflamed colon + mucosal ulcerations	Positive CMV stain on IHC + positive qualitative CMV DNA on stools.	Ganciclovir IV	Resolved
van Turenhout *et al.* [16]	54/F	Lung adenocarcinoma	Nivolumab	Refractory diarrhea	Erosive and friable inflamed colon + mucosal ulcerations	Positive CMV stain on IHC	Not administered	Resolved
Furuta *et al.* [17]	77/M	Melanoma	Nivolumab	Hematochezia and diarrhea	Multiple punched out ulcers	Crypt abscesses plus lymphocyte infiltration with positive CMV stain with IHC.	Ganciclovir IV	Resolved
Kadokawa *et al.* [18]	58 / M	Lung adenocarcinoma	Durvalumab	Bloody diarrhea	Erosive and friable inflamed colon	NA	Ganciclovir 5 mg/kg IV every 12 hours	Resolved

type of ICI, the dosage of the regimen, and the underlying malignancy [8,9]. For instance, the IMC incidence rate in patients receiving CTLA-4 agents is higher compared to those receiving PD1/PD-L1 agents (9%-35% vs. 1%-10%; respectively) [1,8,9]. IMC can occur in up to 32% of patients on a combination therapy [1,8,9]. IMC appears after four weeks in patients receiving CTLA-4 agents and 4-12 weeks in those receiving PD1/PDL-1 agents [8,9]. However, it can occur as early as ten days or as late as two months after the last ICI infusion [8,9].

The symptoms of IMC include mild to severe diarrhea, hematochezia, abdominal distension, abdominal cramping, and flatulence [8,9]. In rare cases, it can lead to severe peritonitis with perforation and septic shock [8]. The American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) guidelines recommend testing for *Clostridium* difficile toxin, fecal calprotectin, and CMV PCR on colonic or stool tissue to rule out infectious etiologies [8,9]. A colonoscopy should be done in patients with diarrhea of grade two or above [8,9]. In the majority of cases, the colonoscopy will reveal an acute mucosal inflammation with intra-epithelial neutrophil infiltration, cryptitis, or crypt abscess on histopathological examination [8,9]. Back to our patients, the diagnosis of ICI-related colitis was based on endoscopic and histopathological findings, plus negative infectious work-up, including C diff studies and stool culture. The colonic tissues were either negative for CMV and EBV viral copies (for patient 1), or positive with a CMV viral load of 1884 IU/mL and EBV viral load of 13,679 IU/mL (for patient 2). Both of our patients responded initially to steroid therapy. However, they were re-admitted with refractory colitis where endoscopic reevaluation revealed persistent acute mucosal inflammation with increased viral loads of CMV and EBV.

There is limited data on CMV colitis in patients with IMC. According to Tay *et al*., only 0.3% of those treated with ICI experienced CMV reactivation, 3.8% of which had CMV colitis [10]. Additionally, Franklin *et al.* showed that five of 41 patients with refractory immune-related colitis had CMV reactivation [11]. CMV reactivation is triggered by the inflammation and the over-secretion of Tumor necrosis factor (TNF) [12]. This justifies the tropism of CMV reactivation to the already inflamed tissue [12]. To the date of writing the manuscript, only 14 cases of CMV colitis in patients on immune checkpoint inhibitors have been reported in the literature. Table 1 summarizes the findings and the outcomes [10,11,13-18].

The diagnosis of CMV colitis requires identifying typical symptoms and evidence of CMV tissue invasion, either through Hematoxylin and Eosin (H&E) stain or Immune histochemistry stain (IHC) [12]. Similar to CMV colitis in patients with inflammatory bowel disease, distinguishing between CMV reactivation and CMV tissue invasion in patients with immune-related colitis is challenging [19]. Specific endoscopic and histological findings, such as new endoscopic findings, the positivity of H & E and IHC or IHC alone, the density of CMV-infected cells, high CMV DNAemia, and CMV PCR in colonic tissue, support the diagnosis of CMV disease [12,19,20]. In our cases, the patient had persistent diarrhea despite being on steroids with high CMV viral loads on the colonic tissue, and positive histopathological findings. Ganciclovir intravenously (IV) is the preferred treatment for CMV disease, although oral valganciclovir may be considered in those who can tolerate oral intake [10]. Reducing immunosuppressive therapy is crucial, if possible, but there is no clear consensus on the duration of antiviral treatment or the need for permanent discontinuation of immunotherapy [10]. Similar to CMV, Epstein-Barr virus reactivation in colonic tissue was found to increase the severity of colitis in patients with inflammatory bowel disease [21,22]. We found only one retrospective study that linked EBV mucosal ulcerations and the severity of IMC for four patients [23]. Thus, EBV reactivation may have a role in exacerbating the symptoms of patients with immune-related colitis. However, there is limited available therapy for EBV reactivation where Rituximab is used to be prescribed in transplant patients.

Conclusions

In conclusion, CMV and EBV reactivation are associated with refractory or severe immune checkpoint inhibitor colitis. It is particularly important to be vigilant for CMV colitis, as treatment options like ganciclovir or valganciclovir are available. However, it's too challenging to differentiate between CMV reactivation versus CMV tissue invasive disease. For that, trending viral loads, checking the H & E and IHC stains, and most importantly, the clinical progress of the patient is needed to decide whether to treat or not. For EBV reactivation, there is limited evidence of its role in exacerbating the symptoms of patients with immune-related colitis, with limited available therapeutic options.

Acknowledgements
Joyce Sanyour and Bassem Awada contributed to the conceptualization of the study and were responsible for drafting the original manuscript, as well as reviewing and editing the final version. Ahmad Matar, Rasha Matar, Nausheen Yaqoub, Ibrahim Al Haddabi, Khalid Al-Baimani, and Issa Qarshoubi provided critical review and editing of the manuscript. All authors read and approved the final manuscript.

Consent
Written informed patient consent was obtained for publication of the data contained in this case report.

Corresponding author
Dr. Bassem Awada
Infectious Diseases Division
Sultan Qaboos Comprehensive Cancer Care and Research Centre
Muscat 123, Oman
Email: drbassemawada1991@gmail.com

Conflict of interests
No conflict of interests is declared.

References
1. Johnson DB, Chandra S, Sosman JA (2018) Immune checkpoint inhibitor toxicity in 2018. JAMA 320: 1702-1703. doi: 10.1001/jama.2018.13995.
2. Pusztai L, Foldi J, Dhawan A, DiGiovanna MP, Mamounas EP (2019) Changing frameworks in treatment sequencing of triple-negative and HER2-positive, early-stage breast cancers. Lancet Oncol 20: e390-e396. doi: 10.1016/S1470-2045(19)30158-5.
3. Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Untch M, Fasching PA, Cardoso F, Andersen J, Patt D, Danso M, Ferreira M, Mouret-Reynier MA, Im SA, Ahn JH, Gion M, Baron-Hay S, Boileau JF, Ding Y, Tryfonidis K, Aktan G, Karantza V, O'Shaughnessy J, KEYNOTE-522 Investigators (2022) Event-free survival with pembrolizumab in early triple-negative breast cancer. N Engl J Med 386: 556-567. doi: 10.1056/NEJMoa2112651.
4. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, Lyon AR, Wick W, Kostine M, Peters S, Jordan K, Larkin J, ESMO Guidelines Committee (2022) Management of toxicities from immunotherapy: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 33: 1217-1238. doi: 10.1016/j.annonc.2022.10.001.
5. Griffiths P, Reeves M (2021) Pathogenesis of human cytomegalovirus in the immunocompromised host. Nat Rev Microbiol 19: 759-773. doi: 10.1038/s41579-021-00582-z.
6. Yu H, Robertson ES (2023) Epstein-Barr virus history and pathogenesis. Viruses 15: 714. doi: 10.3390/v15030714.
7. Agrawal AK, Rajendra A, Noronha V, Joshi A, Patil VM, Menon N, Talreja V, Prabhash K (2020) Cytomegalovirus infection in solid malignancies. Cancer Research, Statistics, and Treatment 3: 19-24. doi: 10.4103/CRST.CRST_112_19.
8. Wang DY, Ye F, Zhao S, Johnson DB (2017) Incidence of immune checkpoint inhibitor-related colitis in solid tumor patients: a systematic review and meta-analysis. Oncoimmunology 6: e1344805. doi: 10.1080/2162402X.2017.1344805.
9. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, Atkins MB, Brassil KJ, Caterino JM, Chau I, Davies MJ, Ernstoff MS, Fecher L, Ghosh M, Jaiyesimi I, Mammen JS, Naing A, Nastoupil LJ, Phillips T, Porter LD, Reichner CA, Seigel C, Song JM, Spira A, Suarez-Almazor M, Swami U, Thompson JA, Vikas P, Wang Y, Weber JS, Funchain P, Bollin K (2021) Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol 39: 4073-4126. doi: 10.1200/JCO.21.01440.
10. Tay KH, Slavin MA, Thursky KA, Coussement J, Worth LJ, Teh BW, Khot A, Tam CS, Yong MK (2022) Cytomegalovirus DNAemia and disease: current-era epidemiology, clinical characteristics and outcomes in cancer patients other than allogeneic haemopoietic transplantation. Intern Med J 52: 1759-1767. doi: 10.1111/imj.15496.
11. Franklin C, Rooms I, Fiedler M, Reis H, Milsch L, Herz S, Livingstone E, Zimmer L, Schmid KW, Dittmer U, Schadendorf D, Schilling B (2017) Cytomegalovirus reactivation in patients with refractory checkpoint inhibitor-induced colitis. Eur J Cancer 86: 248-256. doi: 10.1016/j.ejca.2017.09.019.
12. Anastasopoulou A, Samarkos M, Diamantopoulos P, Vourlakou C, Ziogas DC, Avramopoulos P, Kouzis P, Haanen J, Gogas H (2023) Cytomegalovirus infections in patients treated with immune checkpoint inhibitors for solid malignancies. Open Forum Infect Dis 10: ofad164. doi: 10.1093/ofid/ofad164.
13. Lankes K, Hundorfean G, Harrer T, Pommer AJ, Agaimy A, Angelovska I, Tajmir-Riahi A, Göhl J, Schuler G, Neurath MF, Hohenberger W, Heinzerling L (2016) Anti-TNF-refractory colitis after checkpoint inhibitor therapy: possible role of CMV-mediated immunopathogenesis. Oncoimmunology 18: e1128611. doi: 10.1080/2162402X.2015.1128611.
14. Harris KB, Funchain P, Baggott BB (2020) CMV coinfection in treatment refractory immune checkpoint inhibitor colitis. BMJ Case Rep 13: e233519. doi: 10.1136/bcr-2019-233519.
15. Gueguen J, Bailly E, Machet L, Miquelestorena-Standley E, Stefic K, Gatault P, Büchler M (2019) CMV disease and colitis in a kidney transplanted patient under pembrolizumab. Eur J Cancer 109: 172-174. doi: 10.1016/j.ejca.2018.12.027.
16. van Turenhout ST, Berghuis M, Snaebjornsson P, Wilgenhof S, Burgers JA, Haanen JBAG, van Dieren JM (2020) Cytomegalovirus in steroid-refractory immune checkpoint inhibition-related colitis. J Thorac Oncol 15: e15-e20. doi: 10.1016/j.jtho.2019.07.026.
17. Furuta Y, Miyamoto H, Naoe H, Shimoda M, Hinokuma Y, Miyamura T, Miyashita A, Fukushima S, Tanaka M, Sasaki Y (2020) Cytomegalovirus enterocolitis in a patient with refractory immune-related colitis. Case Rep Gastroenterol 14: 103-109. doi: 10.1159/000506186.
18. Kadokawa Y, Takagi M, Yoshida T, Tatsumi A, Fujita K, Inoue T, Ohe S, Nakai Y, Yamamoto S, Otsuka T, Ishihara R, Isei T, Kumagai T, Nishimura K, Imamura F (2021) Efficacy and safety of Infliximab for steroid-resistant immune-related adverse events: a retrospective study. Mol Clin Oncol 14: 65. doi: 10.3892/mco.2021.2227.
19. Nguyen M, Bradford K, Zhang X, Shih DQ (2011) Cytomegalovirus reactivation in ulcerative colitis patients. Ulcers 2011: 282507. doi: 10.1155/2011/282507.

20. Beswick L, Ye B, van Langenberg DR (2016) Toward an algorithm for the diagnosis and management of CMV in patients with colitis. Inflamm Bowel Dis 22: 2966-2976. doi: 10.1097/MIB.0000000000000958.
21. Zhang H, Zhao S, Cao Z (2022) Impact of Epstein-Barr virus infection in patients with inflammatory bowel disease. Front Immunol 13: 1001055. doi: 10.3389/fimmu.2022.1001055.
22. Andari S, Hussein H, Fadlallah S, Jurjus AR, Shirinian M, Hashash JG, Rahal EA (2021) Epstein-Barr virus DNA exacerbates colitis symptoms in a mouse model of inflammatory bowel disease. Viruses 13: 1272. doi: 10.3390/v13071272.
23. Pugh MR, Leopold GD, Morgan M, Christian AD, Hewett R, Durai D, Wagstaff J, Harris D, Dojcinov SD (2020) Epstein-Barr virus-positive mucocutaneous ulcers complicate colitis caused by immune checkpoint regulator therapy and associate with colon perforation. Clin Gastroenterol Hepatol 18: 1785-1795. doi: 10.1016/j.cgh.2019.09.031.