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CASE REPORT

Severe cytomegalovirus gastritis after pembrolizumab in a patient with melanoma

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ABSTRACT

Immunotherapy has emerged as a standard of cancer treatment, with an increasing number of indications. Recently, opportunistic infections have been reported in several cases in which immunotherapy has led to an increased susceptibility to infection. The present case is the first report of cytomegalovirus (CMV) gastritis occurring in a patient with melanoma during immunotherapy without immune-related adverse events (irAEs) and without the use of immunosuppressant agents.

A 43-year-old woman presented with stage III malignant melanoma. She underwent wide excision of skin, with lymph node dissection, and she started immunotherapy with a 3-week cycle of pembrolizumab. The patient demonstrated stable disease response, and no irAEs were observed during her initial treatment courses. However, after the 9th treatment cycle, she began to experience epigastric pain that worsened significantly, requiring a visit to the emergency centre. Imaging by computed tomography (CT) and integrated positron-emission tomography/CT revealed severe diffuse gastroduodenitis with acute pancreatitis.

Esophagogastroduodenoscopy showed diffuse oozing, hemorrhagic, edematous, and exfoliative mucosa involving the entire gastric wall, defined as acute hemorrhagic gastritis. Biopsies of the gastric wall revealed CMV infection. Those findings were consistent with a diagnosis of CMV gastritis, and the patient received antiviral therapy with ganciclovir. After treatment, she recovered enough to resume immunotherapy.

This case report presents a rare occurrence of CMV gastritis related to immunotherapy. As more patients are treated with immunotherapy, incidences of CMV infections are expected to increase; a high index of clinical suspicion is therefore needed in symptomatic patients.

Key Words Cytomegalovirus gastritis, immunotherapy, pembrolizumab

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BACKGROUND

Immunotherapy has emerged as a standard of cancer treatment for an increasing number of indications, including malignant melanoma[1], non-small-cell lung cancer[2], and mismatch repair–deficient colorectal cancer[3]. The mechanism of immunotherapy involves preventing the initiation of immune-inhibitory signals within activated T cells by blocking the activity of PD-1 on T cells, PD-L1 on tumour cells, and CTLA-4 on antigen-presenting cells[4]. Many clinical trials have contributed to the approval of immune checkpoint inhibitors such as ipilimumab (anti–CTLA-4), pembrolizumab (anti–PD-1), nivolumab (anti–PD-1), atezolizumab (anti–PD-L1), avelumab (anti–PD-L1), and durvalumab (anti–PD-L1) by the U.S. Food and Drug Administration. Those agents have been shown to improve progression-free and overall survival in patients with cancers that have a high proportion of PD-L1 expression on tumour cells, a deficiency of mismatch repair, or a high mutational burden. Pembrolizumab is a widely used PD-1 inhibitor. In patients with non-small-cell lung cancer having PD-L1 expression on at least 50% of tumour cells, response rates as high as 44.8% have been reported with pembrolizumab[5].

Immune-related adverse events (irAEs) are usually related to an upregulated immune system and typically affect skin (rash), endocrine organs (thyroiditis, hypophysitis), gastrointestinal (GI) tract structures (colitis), liver (hepatitis), and lung (pneumonitis). Such events are generally mild enough to be treated with high-dose steroids. However, in rare instances, grade 4 events occur, including neurologic disorders and myocarditis, which could result in fatal outcomes[6]. Additionally, opportunistic infections—invasive aspergillosis, cytomegalovirus (CMV)–induced hepatitis, and *Pneumocystis jiroveci* pneumonia—have been reported in several cases in which immunotherapy was related to increased susceptibility to infection mainly because of immunosuppression after an irAE[7,8].

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Here, we present the case of a patient with malignant melanoma who, despite the absence of immunosuppression for an irAE, developed severe CMV gastritis after treatment with the anti–PD-1 antibody pembrolizumab.

CASE PRESENTATION

A 43-year-old woman with no underlying disease presented with black skin lesions on her back and right upper buttock, and an enlarging non-tender right inguinal mass. A biopsy of the right inguinal lymph node revealed metastatic malignant melanoma. Integrated positron-emission tomography/computed tomography (PET/CT) imaging for staging showed increased ^{18}F-fluorodeoxyglucose uptake in the right external and internal iliac lymph nodes (maximum standardized uptake value: 7.9) and lower back skin (maximum standardized uptake value: 2.6), with no evidence for thoracic metastases. The patient was therefore diagnosed with clinical stage III disease.

The patient underwent wide excision of skin involving her back and right upper buttock, with dissection of the right inguinal and iliac lymph nodes. Located on her back, the primary lesion measured 25×20 mm and 3 mm in depth, with no ulceration (pT3a). The skin lesion located on the right buttock measured 5×5 mm, and 19 of the 26 dissected lymph nodes were confirmed to contain metastases.

Immunohistochemical staining indicated that 10% of the patient's tumour cells expressed PD-L1. Furthermore, molecular study with next-generation sequencing revealed that the tissue had no clinically meaningful mutations, including *BRAF* mutation.

Unfortunately, CT imaging performed 1 month after surgery revealed enlarged lymph nodes in the right common iliac area. The patient subsequently began immunotherapy with a 3-week cycle of pembrolizumab 200 mg. After 3 cycles of therapy, the patient underwent further imaging to evaluate treatment response; repeat CT imaging showed slightly enlarged lymph nodes in the right common iliac chain, within an overall stable disease response according to the Response Evaluation Criteria in Solid Tumors, version 1.1. No irAEs were observed during those treatment courses.

Five months later, the patient began experiencing epigastric discomfort after meals. She was admitted to a local hospital, where she received hydration and treatment for pain. However, her symptoms worsened significantly after the 9th cycle of pembrolizumab, requiring a visit to the emergency centre. The patient was experiencing anorexia, nausea, vomiting, and severe epigastric pain, scoring 7–8 on the visual analogue scale.

On physical examination, the patient had tenderness to palpation of the epigastric area without rebound tenderness. Vital signs were stable, without fever, and laboratory results indicated elevated serum amylase and lipase (313.5 U/L and 485.0 U/L respectively) and a decreased platelet count (52,000/μL).

Contrast-enhanced abdominal CT imaging showed severe edematous wall thickening of the stomach and duodenum suggestive of diffuse gastroduodenitis [Figure 1(B,C)]. Imaging by PET/CT also demonstrated increased ^{18}F-fluorodeoxyglucose uptake in the stomach, duodenum, and pancreas, suggestive of acute gastroduodenitis and pancreatitis without disease progression [Figure 1(D)]. To determine the cause, esophagogastroduodenoscopy was performed, showing diffuse oozing, hemorrhagic, edematous, and exfoliative mucosa in the whole gastric wall

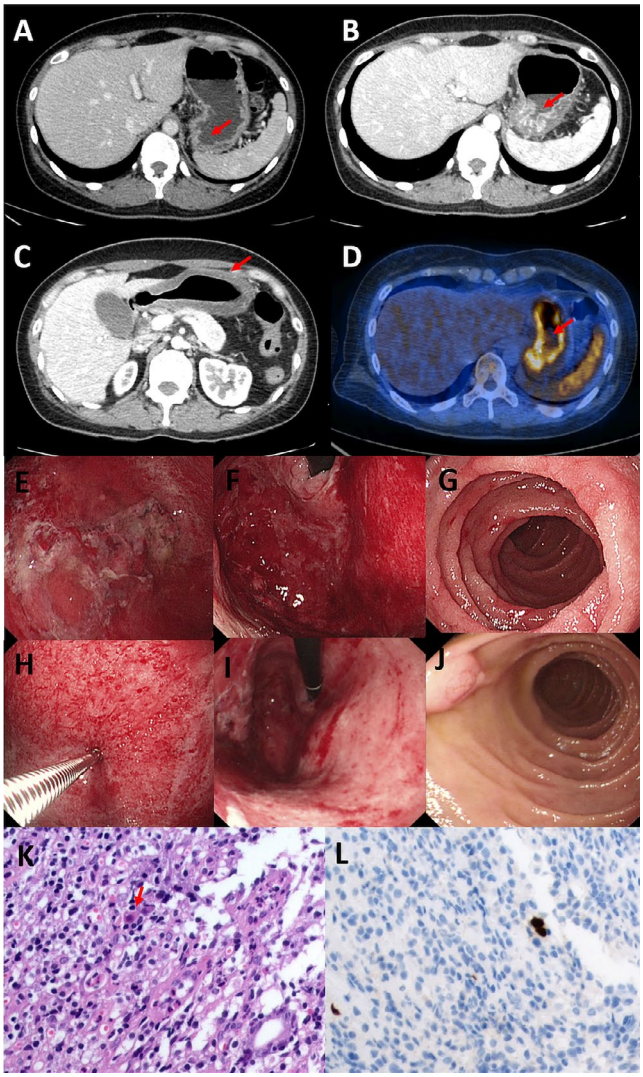

FIGURE 1 Cytomegalovirus (CMV) gastritis after pembrolizumab. (A) Baseline computed tomography (CT) imaging before pembrolizumab shows normal thickening of the gastric wall (arrow). (B,C) After 5 months of pembrolizumab treatment, CT imaging shows severe edematous thickening of the stomach wall (arrow). (D) Integrated positron-emission tomography/CT imaging shows increased ^{18}F–fluorodeoxyglucose uptake at the stomach (arrow). (E,F) Esophagogastroduodenoscopy imaging shows diffuse oozing, hemorrhagic, edematous, and exfoliative mucosa in the entire gastric wall. (G) Edematous and erosive mucosa are seen in the second portion of the duodenum. (H) Biopsies of the gastric wall were obtained, and CMV infection was confirmed. After 1 week of treatment with ganciclovir, much improvement is observed in (I) the diffuse hemorrhagic mucosa of the stomach and (J) the edematous mucosa of the duodenum. (K) Hematoxylin and eosin staining of the gastric biopsy specimens shows CMV inclusions (arrow, 400× original magnification). (L) Immunohistochemistry staining of the same biopsy specimens shows strong brown colour, indicating reactivity to the anti-CMV antibody (400× original magnification).

[Figure 1(E,F)] and several erosions in the second portion of the duodenum [Figure 1(G)]. Those findings, defined as acute hemorrhagic gastritis, were suggestive of an irAE or CMV infection. Biopsies of the gastric wall were obtained [Figure 1(H)].

Before receipt of the final pathology report, the patient was started on steroid therapy with dexamethasone 10 mg because of a high suspicion for irAEs, suggested by the patient's clinical presentation, treatment history, and immune status. However, her symptoms did not improve, and she could not tolerate any food intake.

After 3 days, hematoxylin and eosin staining demonstrated inflamed granulation tissue and necrotic detritus, and CMV infection was confirmed with immunohistochemical staining [Figure 1(K,L)]. The diagnosis of CMV gastritis was then made, and the patient was started on antiviral therapy with ganciclovir 5 mg/kg every 12 hours.

After 1 week of treatment, a follow-up esophagogastroduodenoscopy revealed that the previously noted diffuse hemorrhagic mucosa of the stomach and edematous mucosa of the duodenum were much improved [Figure 1(I,J)]. After 3 weeks of antiviral treatment, the patient had recovered enough to resume immunotherapy.

DISCUSSION

Gastrointestinal toxicity from immunotherapy is a well-described adverse event in many studies. Approximately one third of patients experience diarrhea, and the incidence of colitis ranges from 8% to 22%[9]. Colon perforation occurs in 1%–1.5% of patients with melanoma who are receiving ipilimumab[9,10], and ipilimumab-induced enterocolitis can lead to a fatal outcome in approximately 1.1% of patients[11,12]. However, the upper GI tract is rarely involved. A few case reports of upper GI disorders related to immunotherapy have been published, including acute hemorrhagic gastritis after nivolumab for non-small-cell lung cancer[13] and severe esophagitis and gastritis from nivolumab for malignant lymphoma[14]. Otherwise, involvement of the upper GI tract has been concurrent with severe enterocolitis[9,15].

In most people, CMV causes an asymptomatic and latent infection that persists for the life of the host. Importantly, CMV reactivation is thought to occur regularly throughout the body, requiring constant immune surveillance to prevent disease progression[16]. Thus, CMV disease is a well-known complication in immune-compromised patients or organ transplant recipients. Our case involved a young immune-competent patient experiencing a rare CMV infection after pembrolizumab therapy.

Several studies and case reports have described opportunistic infections after immunotherapy. Del Castillo *et al.*[17] analyzed the occurrence of severe infections after immunotherapy in 740 patients with metastatic melanoma, 54 of whom experienced severe infections involving causes both fungal (2 cases of invasive pulmonary aspergillosis, 3 cases of *P. jiroveci* pneumonia, and 1 case of *Candida* bloodstream infection) and viral (3 cases of zoster infection, 1 case of CMV enterocolitis, and 1 case of Epstein–Barr virus reactivation). However, the main risk factor for infections in those patients was the use of immunosuppressive agents such as corticosteroids and infliximab to manage irAEs after treatment with immunotherapy. The risk of severe infection was 13.5% in patients who had received immunosuppressive agents, but only 2% in those who did not. Also, CMV disease has been related to therapy-refractory immune-related colitis in patients undergoing immunotherapy. Franklin *et al.*[18] reported that 5 of 41 patients with melanoma who developed immune-related colitis after ipilimumab were refractory to standard immunomodulatory treatment, and CMV was detected in all 5 patients. All reported cases of CMV infection occurred in the lower GI tract (enterocolitis, Table I). Our patient with CMV infection of the upper GI tract had not experienced an irAE or received any immunosuppressive agents during her preceding 8 cycles of pembrolizumab.

The recent success of immunotherapy in cancer treatment suggests that the PD-1/PD-L1 pathway might be associated with the prevention and treatment of infectious diseases[21]. However, infections have been reported in patients undergoing immunotherapy, as is demonstrated in our case. That paradoxical event might be explained by the mechanism behind the immune reconstitution inflammatory syndrome seen in patients with AIDS and tuberculosis[22]. In active infection, the PD-1/PD-L1 pathway inhibits the function of CD4 and CD8 effector T cells, preventing a fatal excessive immune response and allowing the pathogen to persist[23]. Blocking the PD-1/PD-L1 pathway with immunotherapy might therefore unmask latent CMV infection by boosting CMV-specific T cell activity.

SUMMARY

Our case highlights a rare instance of CMV gastritis associated with immunotherapy despite the absence of immunosuppression to manage an irAE. As the number of patients treated with immunotherapy increases, incidences of CMV infection are expected to increase, and a high index of clinical suspicion is needed in symptomatic patients. Guidelines for prophylaxis and treatment of such infections are necessary if patients are to continue on immunotherapy.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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TABLE I Overview of cases with cytomegalovirus (CMV) enterocolitis after immunotherapy

Reference	Age	Sex	Histology	Immunotherapy	Onset (weeks)	Symptoms	Immuno-suppressants	Methods	Time of Dx (weeks)	Treatment	
										Type	Duration (weeks)
Lankes *et al.*, 2016[19]	32	Male	Malignant melanoma	Ipilimumab–nivolumab	3	Grade 3 diarrhea, vomiting	Corticosteroid, infliximab	Colon CMV DNA, IHC	9	Ganciclovir valganciclovir	10
Franklin *et al.*, 2017[18]	57	Male	Malignant melanoma	Ipilimumab	13	Grade 3 diarrhea, hematochezia, weight loss	Corticosteroid, infliximab	Colon CMV DNA, IHC	19	Ganciclovir	9
	66	Female	Malignant melanoma	Ipilimumab	7	Grade 3 diarrhea	Corticosteroid, infliximab, cyclosporin	Stool CMV DNA	14	Died	
	67	Female	Malignant melanoma	Ipilimumab	8	Grade 3 diarrhea, hematochezia	Corticosteroid, infliximab	Colon CMV DNA	13	Ganciclovir	3
	77	Male	Malignant melanoma	Ipilimumab	11	Grade 3 diarrhea	Corticosteroid	Colon CMV DNA, IHC	18	Ganciclovir	9
	73	Male	Malignant melanoma	Ipilimumab–nivolumab	8	Grade 3 diarrhea, hematochezia	Corticosteroid, infliximab	Colon and stool CMV DNA	8	Ganciclovir	3
Gueguen *et al.*, 2019[20]	70	Male	Malignant melanoma	Pembrolizumab	12	Grade 3 diarrhea	Corticosteroid	IHC	NA	Ganciclovir valganciclovir	4

Dx = diagnosis; IHC = immunohistochemistry.