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Case Report

Peritoneal Recurrence of Cecal Cancer with Specific Imaging Findings and Shrinkage after Treatment with Pembrolizumab

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Abstract

Pembrolizumab is one of the treatment options for treatment-refractory unresectable advanced or metastatic colorectal cancer with microsatellite instability-high (MSI-H) or deficiencies in DNA mismatch repair (dMMR). Herein, we report a case in which a recurrent cecal cancer lesion showed specific imaging findings and local inflammatory findings during treatment with pembrolizumab, followed by marked shrinkage. The patient was an 80-year-old woman. Postoperative peritoneal recurrence of cecal cancer of approximately 7 cm in size was observed. The patient had MSI-H and was treated with pembrolizumab. After five courses of treatment, the patient presented to our hospital with a chief complaint of abdominal pain. A blood test showed a strong inflammatory reaction, and computed tomography (CT) showed diffuse low-density area in the tumor. Under the suspicion of an abscess, conservative treatment was initiated and the patient quickly recovered. A CT at 1 month showed a marked reduction in size at the same site, and a CT at 3 months showed that the recurrent foci had almost disappeared. The inflammatory reaction before shrinkage in this case may have been caused by tumor immune response to pembrolizumab.

Keywords

colorectal cancer, pembrolizumab, MSI-H, dMMR, peritoneal recurrence

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Introduction

Approximately 5% of stage IV colorectal cancer (CRC) is microsatellite instability-high (MSI-H) and results from the accumulation of high levels of single-base mismatches or short insertions and deletions in repetitive DNA tracts as a result of deficiencies in DNA mismatch repair (dMMR)[1]. MSI-H/dMMR metastatic CRC often originates on the right side of the colon, is poorly differentiated, and is more closely associated with BRAF gene mutation in comparison to microsatellite-stable (MSS) CRC; all factors are associated with poor outcomes. Typically, patients with MSI-H/dMMR metastatic CRC are less responsive to conventional chemotherapy and have a poorer prognosis than patients with mismatch repair-proficient or MSS CRC[2-5]. In this context, the efficacy of pembrolizumab in treatment-refractory unresectable advanced or metastatic colorectal cancer with MSI-H or dMMR was confirmed in an open-label, randomized phase II study (KEYNOTE-164), indicating that it is an important treatment option[6]. However, there are few reports of imaging changes in patients treated with pembrolizumab. Herein, we describe a case in which a recurrent colorectal cancer tumor developed inflammation during pembrolizumab treatment, which was thought to be a tumor immune reaction. The tumor showed remarkable shrinkage after specific imaging findings.

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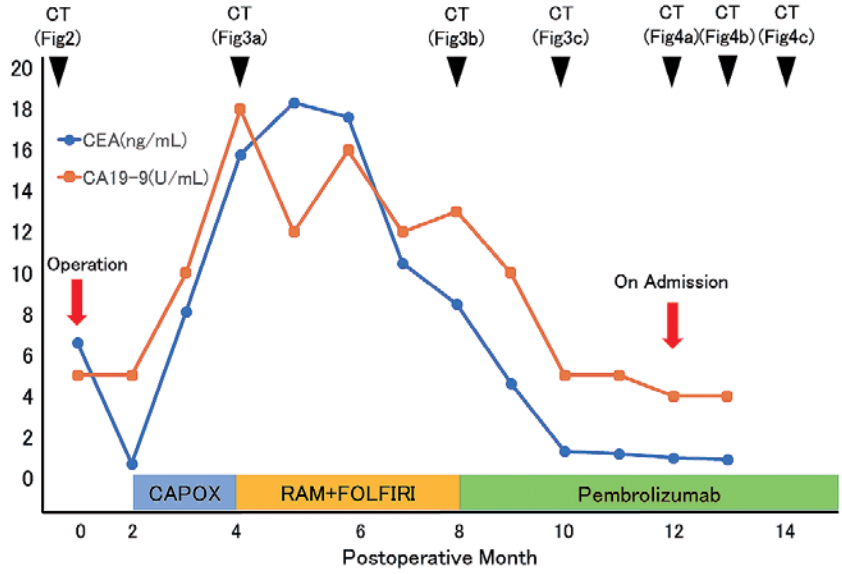

Figure 1.
The course of pembrolizumab from the time of surgery to the time of significant response. The vertical axis is the tumor marker (CEA: ●, CA19-9: ■), and the horizontal axis is the number of months after surgery.

Case Report

The patient was an 80-year-old woman. Her relevant history is shown in Figure 1. She was diagnosed with cecal cancer (preoperative computed tomography (CT) is shown in Figure 2) and underwent open ileocecal resection and D3 lymph node dissection. The pathological results were C, Type5, 13.3 × 10.5 cm, T4b, N0, M0, pStage IIC. The histological type was mucinous carcinoma, and RAS and BRAF were both wild types. Lymphatic invasion (Ly1b) was observed; thus, the disease was classified as high-risk stage II. We decided to administer postoperative adjuvant chemotherapy, and CAPOX (capecitabine 2400 mg/day/body, day 1-14, oxaliplatin 100 mg/body, day 1, day 15-21 off) was initiated. After three courses, CT showed cyst-like structures in the perioperative area on the cephalad and caudal sides (Figure 3a), and the patient's carcinoembryonic antigen (CEA) level was high at 15.8 ng/mL. She was diagnosed with peritoneal recurrence and ramucirumab (RAM, 370 mg) + FOLFIRI (5FU bolus 420 mg/body, civ 1250 mg/body, leucovorin 275 mg/body, irinotecan 200 mg/body) was initiated. Six courses of RAM + FOLFIRI were performed, but the tumor did not shrink (Figure 3b). Considering that the patient had MSI-H, the regimen was changed to pembrolizumab (200 mg). Tumor markers rapidly decreased after pembrolizumab treatment. After three courses of pembrolizumab, CT showed SD, but a small low-density area was found in the cephalic abdominal wall lesion (Figure 3c). Pembrolizumab treatment was continued due to the downward trend of CEA. After five courses of pembrolizumab

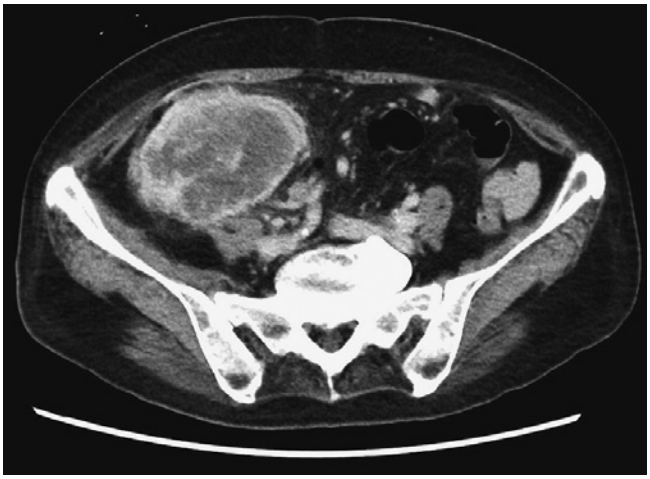

Figure 2.
Preoperative CT showing a bifurcated primary lesion of cecal cancer in the right lower abdomen.

treatment, the patient came to the hospital for chemotherapy and complained of abdominal pain. An abdominal examination revealed mild pain in the right lower abdomen, but no symptoms of peritoneal irritation. Blood tests showed a strong inflammatory response with WBC 8120/μL and CRP 15.64 mg/dL. A CT showed a diffuse low-density area in the cephalic lesion. The same low-density area was also seen in the abdominal wall lesion (Figure 4a). Considering the possibility of gastrointestinal perforation and abscess formation, we decided to admit the patient to our hospital for treatment. The patient was treated conservatively with

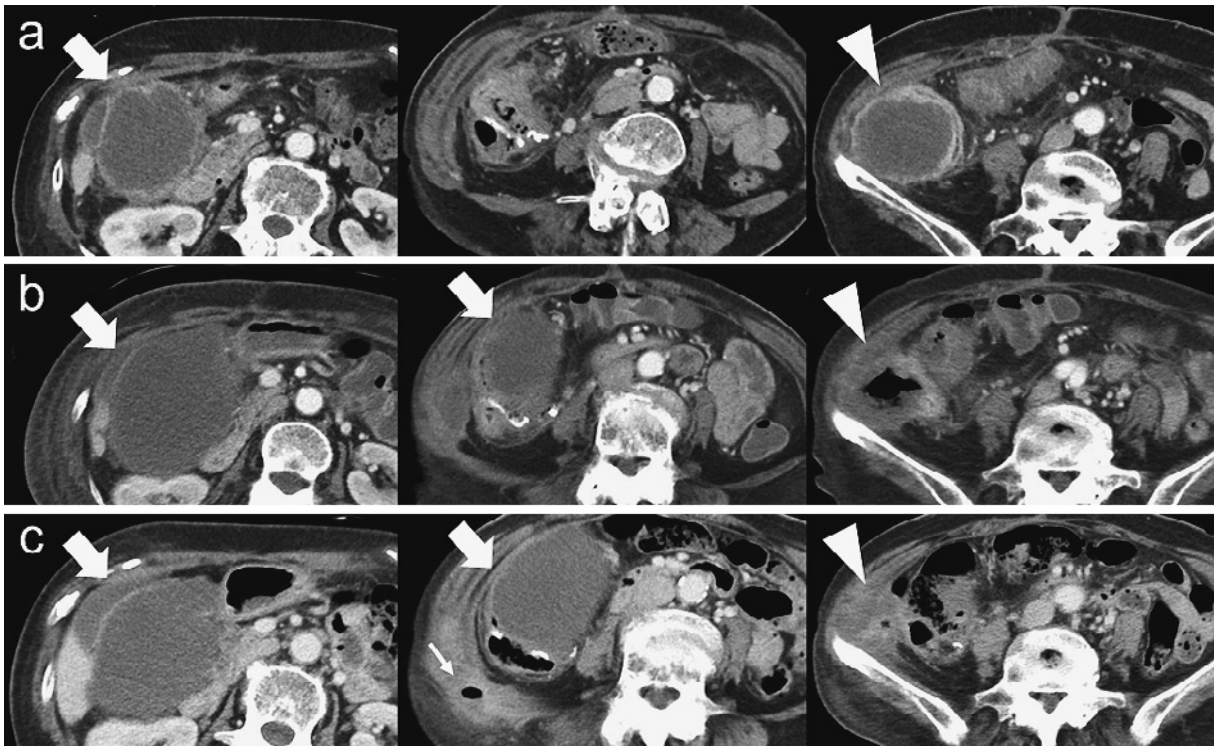

Figure 3.

a: CT after three courses of CAPOX (Cape 2400 mg, OX 100 mg) after surgery, showing a substantial tumor image on the cephalic (thick arrow) and caudal (triangular) sides of the perioperative area, respectively, and a diagnosis of peritoneal recurrence.

b: CT after six courses of RAM + FOLFIRI, tumor was unchanged, switched to pembrolizumab (200 mg) due to MSI-H.

c: CT after three courses of pembrolizumab, showing low-density area in the cephalic abdominal wall lesion despite SD (thin arrow).

fasting and antimicrobial agents, but did not develop fever suggestive of an abscess, and had only mild abdominal pain. We thought it was inflammation caused by tumor and did not perform drainage. Colonoscopy was attempted but was abandoned due to severe pain in the sigmoid colon. The inflammatory response quickly improved, and the patient was discharged from the hospital on the 13th day of hospitalization. The CT at 1 month after discharge showed a marked reduction in the size of all lesions (Figure 4b). Furthermore, the CT at 3 months after discharge showed that the cephalic lesion had almost disappeared and the caudal lesion maintained a shrinking trend (Figure 4c). One year and 10 months have passed since the surgery, and the tumor has maintained a tendency to shrink and no new recurrent metastasis has been observed.

Discussion

This is a case of peritoneal recurrence of colorectal cancer treated with pembrolizumab with specific imaging findings and clinical course followed by shrinkage.

There are two noteworthy points in this case: (1) there was a local inflammatory reaction during the reduction process and specific imaging findings, and (2) the inflammation improved and a CT scan obtained approximately 1 month later showed a marked reduction in size.

In this case, the patient presented with specific CT findings of cavities inside the tumors and inflammatory reaction after five courses of pembrolizumab treatment. The patient was admitted to the hospital for follow-up, and the clinical point of interest is that the patient spontaneously resolved without fever and abdominal pain suspicious of abscess or gastrointestinal perforation. Regarding the first point, the KEYNOTE-164 did not show intra-abdominal abscess as an adverse event of pembrolizumab[6]. Pembrolizumab is a drug that activates the autoimmune response and that has an effect on tumor cells. In our case, we initially suspected infection, but the tumor shrank markedly without invasive procedures such as drainage, and the clinical course showed no fever and very mild abdominal pain, suggesting that it was not an abscess. We initially thought that the changes in the tumor seen on CT were air. However, based on the history of this case, we concluded that there was not air, but cavities caused by necrosis. The fact that the CT scan after three

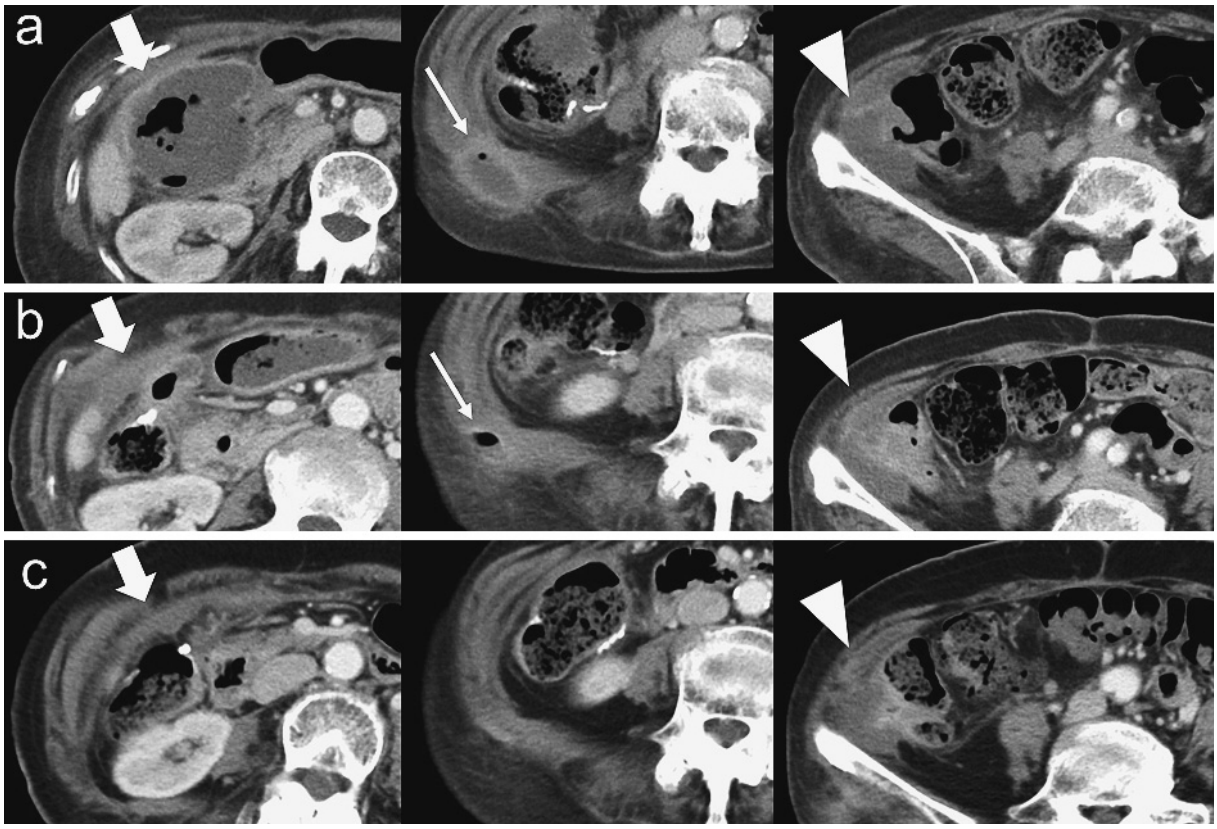

Figure 4.

a: CT of the patient with complaints of abdominal pain after five courses of treatment, showing diffuse low-density area within the substantial tumor in the cephalic lesion (thick arrow). The same lesion was also seen in the abdominal wall lesion (thin arrow).

b: One-month post-discharge CT showed marked reduction in size of all lesions.

c: Three-month post-discharge CT showed that the cephalic and abdominal wall lesions had almost disappeared, and the caudal lesion had maintained its reduction trend.

courses of pembrolizumab already showed cavity within the abdominal wall lesion may also be a basis for denying an abscess. In a report on tumor abscess formation after treatment with pembrolizumab for lung adenocarcinoma, abscess formation was attributed to the association between pembrolizumab and the high expression of PD-L1[7]. There are no reports of abscessed lesions or cavities caused by pembrolizumab in colorectal cancer. However, there are some reports of pembrolizumab-induced necrosis of tumors and formation of cavities inside tumors in lung cancer[8,9]. It is conceivable that the high expression of PD-L1 was the cause of the excessive inflammatory response in this case. The changes observed in this case might be presumed to be the result of tumor necrosis caused by pembrolizumab, resulting in the cavities inside the tumors, which disappeared during the subsequent shrinkage process, as well as abdominal wall lesions after three courses of pembrolizumab.

Regarding the second point, the clinical course of this case suggests that the tumor shrank after the inflammatory response. Immune checkpoint inhibitors shrink tumors by the action of their T lymphocytes. In this case, it is possible that the T lymphocytes became too active and caused inflammation. Immune checkpoint inhibitors are characterized by pseudoprogression and specific side effects, which were first reported in a study on ipilimumab, an anti-CTLA4 inhibitor used in the treatment of melanoma[10]. Later, it was also reported that the pseudoprogression observed in patients treated with pembrolizumab and nivolumab (anti-PD-1 agents) is not true tumor progression, and that it merely caused enlargement in areas with infiltration, edema, and necrosis of immune cells, such as cytotoxic T lymphocytes in the tumor periphery[11]. Furthermore, it has been suggested that a delayed immunological response in addition to the inflammatory response due to tumor infiltration by immune cells may play some role in pseudoprogression[12]. However, the precise mechanism of pseudoprogression remains unknown. In this case, the risk of tumor dissemination due to invasive procedures such as drainage and biopsy was avoided by careful follow-up. Although it may be difficult to distinguish the tumor from an abscess, it is important to

keep tumor necrosis in mind while administering pembrolizumab.

We have experienced a case of recurrent colorectal cancer with marked shrinkage after specific clinical and imaging findings during treatment with pembrolizumab. It is possible that some patients treated with pembrolizumab may experience shrinkage after a local inflammatory response due to its pharmacological effects.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

All authors have contributed to this manuscript and reviewed and approved the current form of the manuscript to be submitted.

Approval by Institutional Review Board (IRB)

Not applicable.

Informed Consent

Written informed consent was obtained from the patients.

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