

Deficient Mismatch Repair Jejunal Cancer Hyperprogression with Pembrolizumab

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ABSTRACT Pembrolizumab is used as a tumor-agnostic drug in deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) tumors. Jejunal cancer is an uncommon type of gastrointestinal cancer, and mismatch repair deficiency is rare in these tumors. In this study, we presented the first case of dMMR/MSI-H jejunal cancer that progressed rapidly following pembrolizumab treatment. Six courses of adjuvant capecitabine and oxaliplatin were administered to a 58-year-old male patient diagnosed with dMMR/MSI-H T4N2 jejunal adenocarcinoma. To treat the progressive disease, pembrolizumab was initiated, and after two cycles of treatment, diffuse tumoral spread occurred in the bilateral lung and mediastinum. Eight days after the drug was discontinued, the patient died due to respiratory failure. In rare tumors, unresponsive patients are not adequately covered. Administering pembrolizumab may lead to rapid progression of dMMR/MSI-H jejunal cancer.

Keywords: Immune checkpoint inhibitors; pembrolizumab; progression; jejunal cancer

Immune checkpoint inhibitors (ICI) are promising agents for treating metastatic colorectal cancer.¹ In deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) tumors, pembrolizumab treatment is recommended as the second-line treatment or administered even later. The results of studies on colorectal and non-colorectal dMMR/MSI-H groups suggested that these agents might be effective in rare gastrointestinal tumors.² However, rare tumors, such as jejunal cancer, are underrepresented in clinical trials involving ICIs. While there were only two small bowel carcinomas reported in one of the studies on pembrolizumab, an effective response rate could not be recorded in another Phase II study.^{2,3} A study reported a dMMR/MSI-H jejunum cancer case, with rapid treatment response following the administration of pembrolizumab.⁴ In this article, we presented the first case of dMMR/MSI-H jejunal cancer with rapid clinical deterioration after treatment with pembrolizumab.

CASE REPORT

A 58-year-old male patient diagnosed with celiac disease was admitted to Hacettepe University Hospital with complaints of abdominal pain, nausea, and vomiting. An occlusive lesion and mesenteric lymphadenopathy were found in the jejunum; however, no systemic involvement was detected in contrast-enhanced thoracic and abdominal computed tomography (CT) scans. Endoscopic examinations showed a large, irregular, and ulcerated jejunal lesion with circumferential bowel wall involvement. Whether the condition was benign or malignant could not be determined, and the patient underwent surgery to treat intestinal obstruction. Histopathological examinations revealed CK20-negative, CK7, CDX2, and EMA-positive invasive, moderately differentiated adenocarcinoma of the jejunum. Nine of the 13 lymph nodes removed were metastatic, and the loss of expression of MLH1 and PMS2 was detected immunohistochemically.

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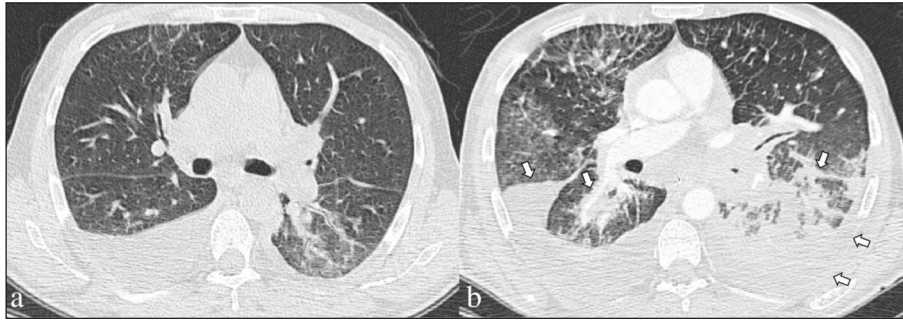


FIGURE 1: Thoracic computed tomography images before (a) and after (b) treatment with pembrolizumab.

After the patient was diagnosed with dMMR/MSI-H T4N2 jejunal adenocarcinoma, six courses of adjuvant capecitabine and oxaliplatin were administered to the patient. Following this, thoracic and abdominal CT scanning was performed, and the scans showed growing pleural effusion and newly developed large lymphadenopathies adjacent to the surgical site. Cytological examinations of the pleural fluid were compatible with adenocarcinoma metastasis. Then, a treatment regimen was planned in which 200 mg of pembrolizumab was scheduled to be administered at 21-day intervals. After two courses of pembrolizumab treatment, the patient's general condition worsened, and respiratory distress developed. There was no growth in sputum aerobic and fungal cultures, and the results of the coronavirus disease-2019 polymerase chain reaction and respiratory pathogen panel analyses were negative. Brain natriuretic peptide was within normal limits, and no signs of heart failure were detected via bedside echocardiography. In the thoracic CT scan, tumor infiltration was detected in the lower lobes, mediastinal, and left hilum, and left supraclavicular enlarging lymphadenopathies and lymphangitic spread were observed (Figure 1). Subsequently, pembrolizumab was discontinued, and the patient was admitted to the ward for supportive care. However, eight days later, the patient died of respiratory arrest.

Written informed consent for publication was obtained from the patient's first-degree relatives.

DISCUSSION

ICIs are used effectively, especially for treating malignant melanoma and renal cell carcinoma, and are

associated with high overall survival.⁵⁻⁷ Because rare tumors are underrepresented in immunotherapy clinical trials, making category I recommendations in the treatment guidelines is challenging. As effective alternative strategies for treating rare tumors are lacking, immunotherapeutic agents are used based on the inferences of other studies. However, Phase III studies have not been conducted on these tumors, and generalizations are made with a limited number of patients in basket studies.

Pembrolizumab is administered for treating dMMR/MSI-H tumors independent of histology, and only two cases of small bowel carcinoma in Phase II clinical trials have been reported.² In a multicenter Phase II study (ZEBRA), 40 patients with previously treated advanced small bowel adenocarcinoma were administered 200 mg of pembrolizumab intravenous every three weeks. Only four (10%) patients included in that study had MSI-H tumors. After a median of four (range, 1-35) cycles, death or progression occurred in 85% of the patients, and a confirmed partial response was detected in only three patients (two of whom had MSI-H tumors). Irrespective of the location of the small bowel, overall survival and progression-free survival were 7.1 and 2.8 months, respectively.³

While dMMR/MSI-H tumors are considered to be associated with late metastasis in early-stage tumors, they can be used to predict immunotherapeutic responses in advanced stages.^{1,8} However, in some patients who were administered immunotherapy, early unresponsiveness and rapid progression were observed. The etiology of this condition, defined as hyperprogression, needs to be further evaluated.^{9,10}

Patients with rare tumors were generally found to show excellent response to immunotherapy, probably because unresponsive patients were under-reported. In conclusion, patients with dMMR/MSI-H jejunal cancers might undergo rapid progression after treatment with pembrolizumab. Further studies with a large number of patients are needed to investigate the effectiveness of immunotherapy in small bowel cancer.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Hasan Çağrı Yıldırım; **Design:** Deniz Can Güven; **Control/Supervision:** Ömer Dizdar; **Data Collection and/or Processing:** Hasan Çağrı Yıldırım, Elvin Chalabiyev; **Analysis and/or Interpretation:** Hasan Çağrı Yıldırım, Rashad Ismayilov; **Literature Review:** Rashad Ismayilov; **Writing the Article:** Hasan Çağrı Yıldırım, Rashad Ismayilov; **Critical Review:** Deniz Can Güven, Ömer Dizdar; **References and Fundings:** Elvin Chalabiyev; **Materials:** Hasan Çağrı Yıldırım.

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