Complete response to neoadjuvant pembrolizumab and capecitabine in microsatellite stable, Epstein-Barr virus-positive, locally advanced gastric adenocarcinoma: case report

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Abstract: Immunotherapy has been established as a standard in select molecular subgroups of treatment-refractory advanced gastric cancer. However, its role in resectable gastric cancer where perioperative systemic therapy is the standard remains unclear. We present a case of a man who was diagnosed with resectable gastric cancer that was microsatellite stable but programmed death-ligand 1 (PD-L1) and Epstein-Barr Virus (EBV)-positive. Given extenuating circumstances of the SARS-CoV-2 pandemic, preferences to limit exposure to the healthcare setting, and the unique tumor molecular features, neoadjuvant pembrolizumab and capecitabine was pursued after multidisciplinary discussion. He was able to achieve a complete response to this neoadjuvant regimen with no further signs of radiographic or pathologic disease on follow-up. We highlight a dramatic response to this novel approach that represents among the first cases to support a potentially viable neoadjuvant chemoimmunotherapy strategy to resectable gastric cancer. In select patients, perioperative immunotherapy-based therapy may constitute a promising strategy in resectable gastric cancer and warrants further investigation.

Keywords: Gastric cancer; neoadjuvant therapy; pembrolizumab; Epstein-Barr virus; immunotherapy; case report

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Introduction

Gastric cancer is the fifth most common cancer by incidence and third highest in mortality worldwide (1). For early-stage disease, the only curative option continues to be surgical or endoscopic resection, with a 5-year survival rate of 69.5% for localized disease in the United States (2). For clinical ≥ T2 or node-positive, locally advanced disease, perioperative 5-fluorouracil-based regimens (e.g., FLOT or FOLFOX) represent current treatment standards (3,4). Pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor is currently approved in treatment-refractory unresectable locally advanced, recurrent, or metastatic gastric cancer programmed death-ligand 1 (PD-L1) positivity by combined positive score (CPS) or microsatellite instability (MSI)/mismatch repair deficiency (dMMR) (5,6).

This report demonstrates a successful case of treating a resectable gastric cancer with only a traditionally neoadjuvant regimen. PD-1 inhibitors are currently limited to use in the metastatic setting, and their benefit in non-metastatic gastric cancer (i.e., neoadjuvant and/or adjuvant) has not been definitively established. Furthermore, there is an active search to identify other immunogenic biomarkers

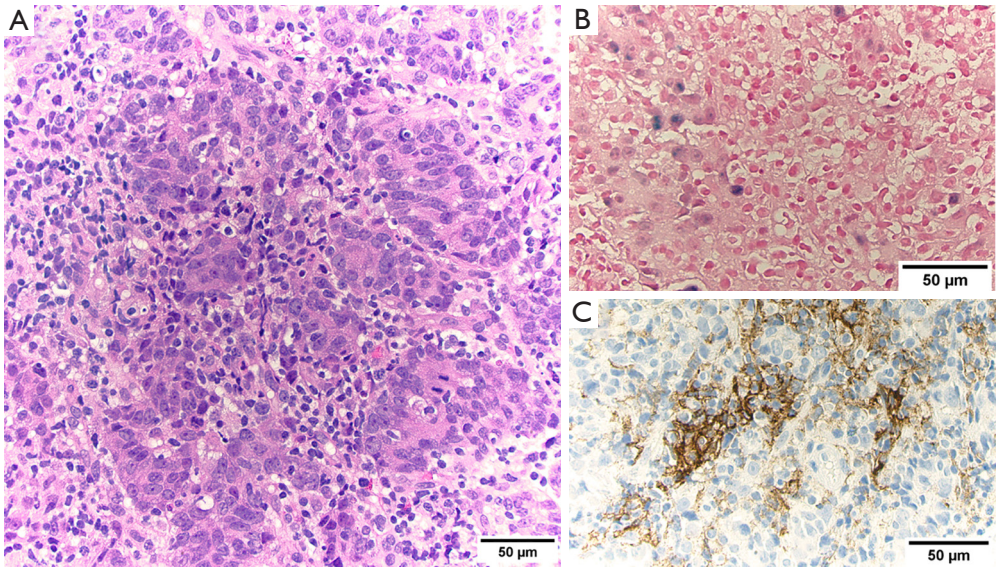

Figure 1 Pathology images of the gastric malignancy. (A) H&E-stained histologic sections reveal a poorly differentiated carcinoma with rare poorly-formed glands and a dense lymphoid infiltrate. (B) In-situ hybridization shows patchy nuclear EBV-positivity in the tumor. (C) Immunohistochemistry for PDL-1 demonstrates strong membranous staining of tumor cells and immune cells (CPS of 40).

to support the use of checkpoint inhibitors in gastric cancer.

We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/acr-21-11).

Case presentation

A 78-year-old man presented to the emergency department with hematemesis and melena. Previous medical history was unremarkable for liver pathology or GI malignancy. Additionally, he was a non-smoker and did not report notable alcohol consumption. On Day 0, upper endoscopy revealed a 3 cm friable mass in the gastric cardia; hematoxylin-and-eosin (H&E) stained histologic sections of the biopsy results confirmed poorly differentiated gastric adenocarcinoma with tumor cells associated with a prominent lymphoid infiltrate (*Figure 1A*). Helicobacter pylori was identified. Additional studies were notable for Epstein-Barr encoding region (EBER) in-situ hybridization positivity (*Figure 1B*). Immunohistochemistry showed intact nuclear expression for mismatch repair proteins (MLH1, PMS2, MSH2 and MSH6) indicative of microsatellite stability (MSS). The formalin-fixed, paraffin-embedded tumor tissue was evaluated utilizing the DAKO FDA-approved PD-L1, 22C3 pharmDX™ protocol using the Dako Automated Link 48 platform. PD-L1 protein expression is determined by using CPS, which is the number of PD-L1 staining cells divided by the total number of viable tumor cells and then multiplied by 100. PD-L1 staining cells is defined as: tumor cells showing partial or complete membrane staining at any intensity plus PD-L1 staining in tumor infiltrating or tumor adjacent mononuclear inflammatory cells (lymphocytes and macrophages) with membrane and/or cytoplasmic staining at any intensity. A specimen with CPS ≥1 is considered to have PD-L1 expression. The patient's tumor had a high CPS of 40 (*Figure 1C*). Staging work-up was negative for metastatic disease, and the plan was made to start neoadjuvant systemic therapy followed by resection and adjuvant therapy for cT2N2M0 disease (Day 54).

In the extenuating circumstances of the SARS-CoV-2 pandemic, the patient preferred to limit his exposure to the hospital environment. Given this preference and the tumor's unique features, a multidisciplinary decision was made to trial a neoadjuvant therapy regimen that would minimize SARS-CoV-2 exposure and frequency of infusion visits, while maintaining safety and efficacy of the regimen. As such, the patient was started on pembrolizumab (200 mg intravenous) and capecitabine (850 mg/m^2 oral twice daily for 14 days) every 3 weeks for the first 2 cycles, followed by spacing out the pembrolizumab (400 mg) to every 6 weeks onward per tolerability (Day 54, 76, 97). Capecitabine was

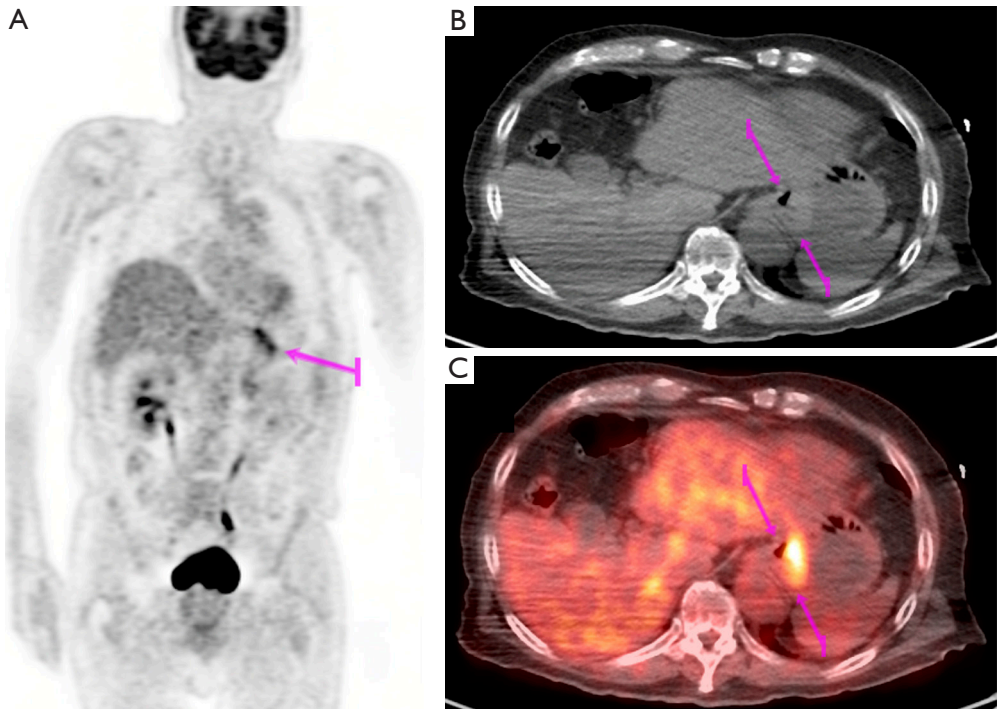

Figure 2 PET/CT imaging of gastric malignancy prior to neoadjuvant therapy. Coronal PET (A), Axial CT (B) and Axial Fused PET/CT (C) images circumferential wall thickening involving the gastric cardia with associated hypermetabolism (arrows) compatible with a primary gastric malignancy.

held on cycle #4 due to neutropenia but pembrolizumab was continued (Day 118). After receiving 4 cycles of neoadjuvant therapy, the patient underwent repeat imaging, endoscopy and biopsies showing complete radiographic and pathologic resolution of the cancer (*Figures 2,3*). A complete pathologic response was documented by upper GI endoscopy with no evidence of cancer on multiple biopsies (Day 154). Given the dramatic response both radiographically and pathologically—with mapping GI endoscopy—as well as the patient's wish to avoid total gastrectomy as well as high surgical risk candidate in a 78-year-old man, we opted for surveillance rather than surgery. The patient continued on maintenance pembrolizumab (400 mg every 6 weeks for 1 year) and surveillance. At the time of this report, which has been nearly a year from the time of starting neoadjuvant therapy, the patient remains in complete remission and has not experienced any adverse events or unanticipated interruptions to his care (*Figure 4*).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Discussion

We present a unique case of complete response to neoadjuvant chemoimmunotherapy in a patient with MSS, PD-L1-positive, and EBV-positive locally advanced gastric cancer deemed otherwise medically inoperable. There are similar case reports of partial response of locally advanced gastric cancer to neoadjuvant nivolumab (7). However, the current clinical guidelines recommend chemotherapy rather than immunotherapy in the perioperative setting for locally advanced gastric adenocarcinoma (8). FOLFOX or FLOT are the most commonly used regimens in this scenario. PD-1 blockade is currently only approved in advanced gastric cancer patients with MSI who are refractory to standard therapies and those following progression on ≥ 2 systemic therapies with tumors that are PD-L1 positive (CPS ≥1) (5,6). More recently, nivolumab was U.S. Food and Drug Administration (FDA) approved for the second-line treatment of advanced esophageal squamous cell carcinoma (ESCC) after fluoropyrimidine- and platinum-based

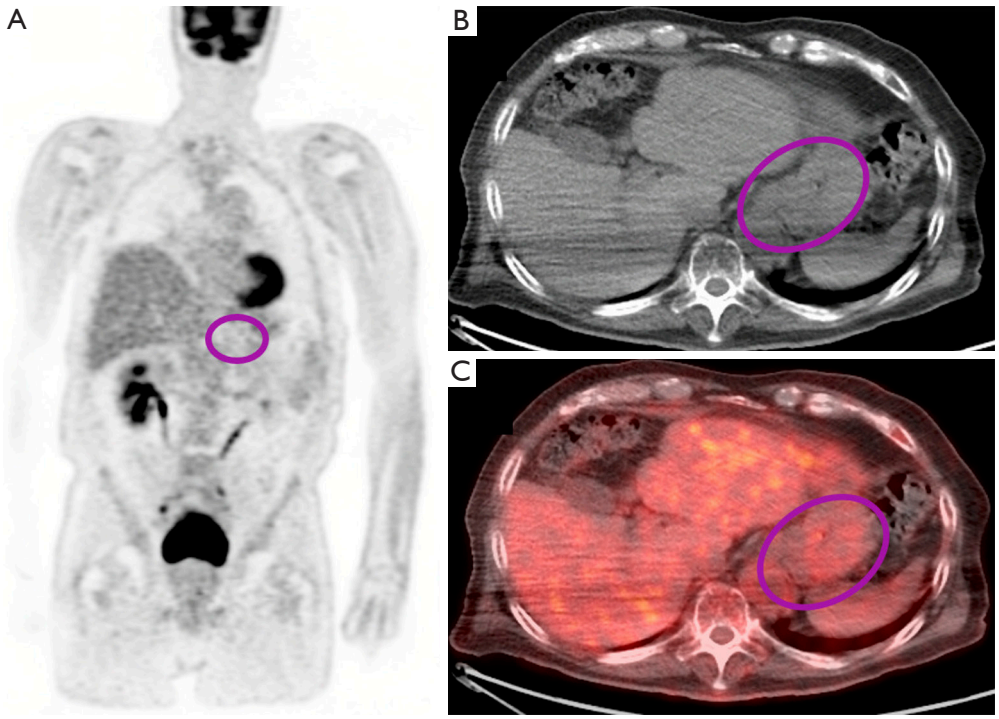

Figure 3 PET/CT imaging of non-detectable gastric malignancy after neoadjuvant immunotherapy. Coronal PET (A), Axial CT (B) and Axial Fused PET/CT (C) images demonstrate interval resolution of the previously noted hypermetabolic circumferential wall thickening involving the gastric cardia (circled).

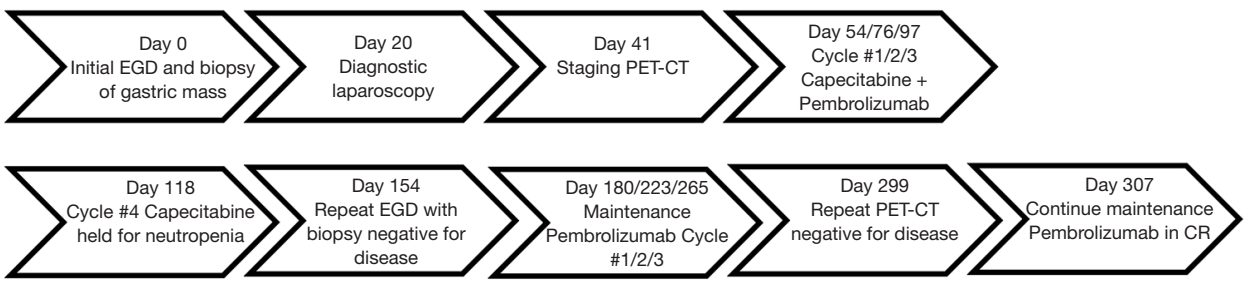

Figure 4 Summary timeline of major events starting from time of initial tumor biopsy.

chemotherapy based on results of ATTRACTION-3 (9). Immunotherapy is not approved in the non-metastatic gastric cancer setting.

There were multiple indications that suggested our patient would have a favorable response to immune checkpoint inhibition. Tumor microsatellite instability and PD-L1 positivity are the conventional predictors of response to immunotherapy in gastric cancer. Our case demonstrated high PD-L1 expression (CPS 40), whereby prior phase III evidence has shown that the benefit of pembrolizumab over chemotherapy is significantly pronounced in the first- or second-line treatment of advanced gastroesophageal cancer when PD-L1 CPS is ≥10 (10).

However, our case also demonstrated EBV-positivity in the setting of MSS status. Recently, molecular profiling of metastatic gastric tumors treated by PD-1 inhibition in a single-arm phase II study demonstrated that high microsatellite instability and EBV positivity were each strongly correlated with exceptional response rates of 85.7–100% (11). Importantly, cases of EBV-positive

metastatic gastric cancer were exclusive to those with MSI tumors in this study. Pathologic review in our case also identified a prominent tumor lymphoid infiltrate. Tumor-infiltrating lymphocytes (TILs) have also emerged as a predictive biomarker for immune checkpoint inhibition across multiple solid tumors and have been associated with a gene inflammation signature and high tumor mutational burden (TMB) (12). Interestingly, in EBV-associated gastric cancer, TIL-positivity has been associated with a positive prognosis (13). In summary, although our patient's dramatic response to neoadjuvant pembrolizumab occurred in the setting of PD-L1 positivity, there were other features including EBV-positivity and TILs that likely contributed to a robust antitumor immune response in an otherwise MSS tumor. Consequently, a limitation of this case is the baseline immunogenicity of this patient's tumor may predispose him to better outcomes to immunotherapy.

Pressure from a global pandemic to decrease the frequency of infusions and clinic visits catalyzed our decision to trial chemo-immunotherapy as neoadjuvant therapy. We are not yet aware of any data demonstrating the objective response rates to neoadjuvant immunotherapy in gastric cancer. In terms of major clinical trials investigating pembrolizumab in metastatic gastric cancer, KEYNOTE-059, KEYNOTE-61, and KEYNOTE-62 have previously reported complete response rates of 2.3%, 4%, and 3.5% respectively (5,10,14). However, there are now ongoing randomized, double-blinded, multicenter Phase III trials such as KEYNOTE-585 investigating the efficacy of pembrolizumab with or without chemotherapy in the perioperative treatment of localized gastric adenocarcinoma (15). If the evidence proves robust, the role of immunotherapy in the neoadjuvant treatment of gastric adenocarcinoma may continue to expand in the future. Our case lends support to this novel treatment paradigm where perioperative immunotherapy-based approaches could be offered in select patients with resectable gastric cancer.

In summary, the key take-away lessons from this case include the possible use of neoadjuvant immunotherapy in place of surgery for limited cases of gastric cancer, the curative potential of PD-1 blockade in patients with limited tumor burden, and adaptation of treatment plans for individual and societal circumstances. With further investigation of the efficacy of neoadjuvant immunotherapy, then we may have another treatment option to offer patients who would not tolerate or qualify for surgical interventions.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/acr-21-11

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/acr-21-11). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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