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Case Report
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Successful Treatment of Metastatic Gastric Carcinoma Deficient in Mismatch Repair Proteins with Immune Checkpoint Blockade: A Case Report and Review of the Literature

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Abstract

Treatment of locally advanced and metastatic gastric cancer has continued to be challenging and overall prognosis from this disease has remained poor with conventional chemotherapy. Through prospective and retrospective investigations, gastric carcinomas deficient in mismatch repair proteins have proven to be responsive to immune checkpoint blockade in the metastatic setting. We present a case of a patient with diffuse peritoneal metastatic gastric carcinoma and deficient in mismatch repair proteins who is effectively treated with single agent immune checkpoint blockade. This case is of interest as we have interval biopsy of disease demonstrating a robust inflammatory response within the tumor stroma and over 17 months of response and dramatic improvement in performance status while on immunotherapy. While this may only be applicable to a small subgroup of patients it represents a therapy with significant improvement in anti-tumor activity compared to conventional chemotherapy. This also highlights the importance of checking clinically meaningful biomarkers as well as the need to identify science-based tumor and patient specific markers that will allow us to better select treatment for each patient in the future.

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Introduction

Treatment of locally advanced and metastatic gastric cancer has continued to be challenging and overall prognosis from this disease has remained poor with conventional chemotherapy. Better understanding of the biologic and genetic characteristics of the disease has led to improvement in treatment with targeted therapy in a very select patient population. For instance, Her-2 overexpression and gene amplification was first described in the 1980s [1]. Subsequently, the anti-HER-2 monoclonal antibody trastuzumab demonstrated improvement in objective response rates when added to standard chemotherapy compared to patients treated with standard chemotherapy alone for treatment of metastatic or locally advanced gastric or gastroesophageal junction cancers [2]. There is an unmet need to identify more patients' specific, cancer biology-based treatment options including immune and pathway based therapies [3].

Mismatch Repair (MMR) proteins play a key role in recognizing and eliminating DNA errors [4]. A loss of these key MMR proteins (deficiency, dMMR; microsatellite instability high, MSI-H) which leads to a marked increase in mutations and therefore increases the Tumor Mutational Load (TML). Malignancies with dMMR have high numbers of somatic mutations and this leads to a marked increase in abnormal proteins-Tumor Mutational Burden (TMB) that have the potential to instigate an adaptive immunogenic response [4,5].

It is postulated that because of this large number of potential proteins and therefore cancer antigens, tumors dMMR are more likely to be responsive to immune checkpoint blockade, which de-suppresses the potential existing anti-tumor immune reaction. Prospective and retrospective analysis of dMMR tumors consistently demonstrates response to immune checkpoint blockade across disease subtypes [5,6].

In gastric carcinoma it is estimated that approximately 8% of tumors have dMMR proteins. Most of these patients have loss of MLH1 and PMS2 [7]. While this represents a small subset of patients with gastric carcinomas, this demonstrates a potential targeted treatment strategy.

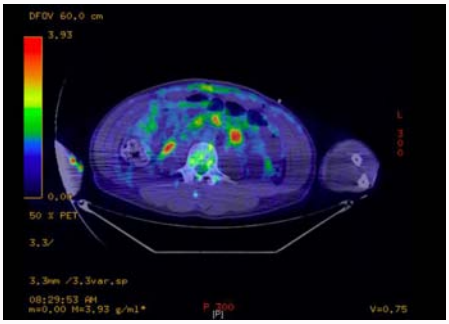

Figure 1: Pretreatment PET/CT demonstrating several scattered areas of hypermetabolic activity noted throughout the mesentery and peritoneal space with maximum SUV of 8.07.

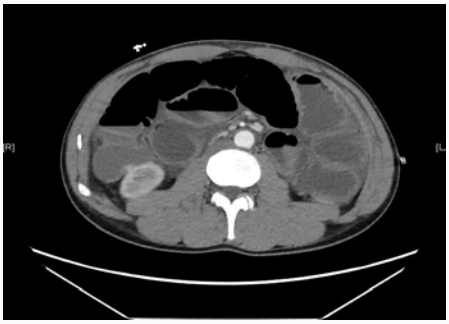

Figure 2: CT abdomen demonstrating multiple dilated fluid and air filled loops of small bowel compatible with small bowel obstruction caused by diffuse peritoneal involvement by carcinoma.

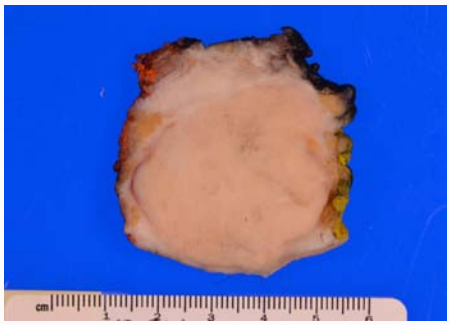

Figure 3: Gross specimen from abdominal wall demonstrating a well circumscribed tan lesion. All margins were free of tumor cells.

Several monoclonal antibodies have been developed to block the interaction between PDL-1 on tumor cells and PD-1 on T cells. This disruption allows the activated T cell to recognize and initiate an immune response against tumor cells and has been used in a variety of cancer subtypes.

Pembrolizumab is a monoclonal antibody against PD-1. Efficacy was evaluated in Keynote 059, and objective response rates to immunotherapy in patients with previously treated advanced Gastric or Gastroesophageal Junction Cancers (G/GEJ) was around 11% in the general population irrespective tumor characteristics.

However, in the cohort who was identified as having dMMR or MSI-high tumors had improved overall response which in over half of the patients with metastatic disease who were treated previously responded to treatment was maintained beyond 6 months [8].

We present a case of diffuse peritoneal metastatic gastric carcinoma with dMMR that is effectively treated with single agent pembrolizumab. This case is of interest as we have interval biopsy of disease demonstrating a robust inflammatory response within the tumor stroma and over 17 months of response and dramatic improvement in performance status while on immunotherapy.

Case Presentation

A 29-year-old male with no significant past medical history presented to his primary care physician with a two-month history of abdominal pain, early satiety, bloating, nausea and vomiting. After failing treatment for suspected gastroesophageal reflux disease and aggressive worsening of clinic performance status and symptoms, he was referred for endoscopy. He underwent Esophagogastroduodenoscopy (EGD) and was found to have a large infiltrative bleeding mass on the lesser curvature of the stomach just below the cardia. Biopsy confirmed poorly differentiated adenocarcinoma consistent with gastric origin. His staging endoscopic ultrasound demonstrated T2N1Mx disease and subsequent PET-CT scan demonstrated diffuse peritoneal carcinomatosis with clinical concern of high risk for bowel obstruction (Figure 1 and 2). He was quickly started on standard chemotherapy with FOLFOX while a detailed pathology analyses were pending for review at our institution.

Three days after his first cycle of FOLFOX he was admitted for malignant small bowel obstruction and underwent emergent small bowel resection. The surgeon discovered extensive peritoneal disease and carcinomatosis with multiple areas of stricturing of the small bowel. There were also multiple masses palpable along the greater curvature of the stomach. He had significant anorexia, ongoing weight loss and was started on enteral feeding. By this time the pathology analysis results were available, which demonstrated that his tumor was HER2-negative but had loss of expression of MLH1 and PMS2 with PDL1 of 5% and therefore dMMR. Of note germline genetic testing performed later is negative.

Based on dMMR, he was started on Pembrolizumab 200 mg IV Q 3 weeks and aggressive postoperative supportive care. Approximately 4 to 6 weeks after starting treatment he had marked improvement in his symptoms and was able to transition off enteral feeding. His clinical performance status improved from ECOG 3 to 0 after 3 doses of Pembrolizumab and images showed great response to therapy. Restaging imaging remained stable for approximately 6 months after initiating immunotherapy.

During a returning visit 8 months after starting Pembrolizumab, he reported development of a mild, tender, erythematous, soft nodule along the midline abdominal wall incision site which measured approximately 2.5 cm. Repeat images demonstrated 'likely progression' only at the midline abdominal wall mass, without evidence of disease progression in the rest of the body. The patient's overall performance remained excellent and empiric antibiotics were given, which did not lead to improvement of the lesion.

After multidisciplinary disease group discussion regarding biopsy versus resection, he underwent complete resection. He also had exploratory laparoscopy at that time which showed complete resolution of previously demonstrated diffuse peritoneal carcinomatosis.

Although the nodule itself demonstrated gastric adenocarcinoma based on the pathology study the abdominal wall mass showed that the cancer component was only localized in the mid of the mass

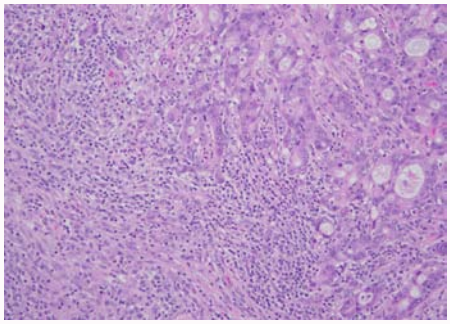

Figure 4: Hematoxylin and eosin staining 10x demonstrating peritumoral lymphocytes at the tumor (upper right) and stroma (lower left).

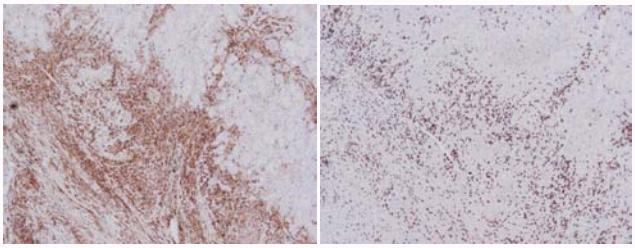

Figure 5: Peritumoral lymphocytes staining positive for CD4 (left) and CD8 (right) demonstrates a mixed inflammatory response.

mixed with dense inflammatory infiltrate. Examination demonstrated an abundance of peritumoral lymphocytes with admixed histiocytes at stroma demonstrated by positive CD4 and CD8 staining (Figures 3-5). All margins were free of cancer.

Based on negative laparoscopy and dense inflammatory infiltrate of his anterior abdominal wall mass he was continued on immunotherapy. Subsequent repeat imaging demonstrated almost complete resolution of disease. He had repeat EGD one year after initiating immunotherapy which demonstrated a small gastric ulcer. This was biopsied, and pathology demonstrated no carcinoma but marked acute and chronic inflammation. He has been receiving Pembrolizumab for over 17 months and imaging has remained the same.

Discussion

This case confirms effective treatment of dMMR gastric cancer with immune checkpoint inhibitor. Keynote 061 was a randomized controlled trial which compared pembrolizumab *vs.* paclitaxel for previously treated advanced gastric or gastroesophageal junction cancers. Median overall survival was 9.1 months in the pembrolizumab *vs.* 8.3 months in the paclitaxel arm and therefore a negative study when applied to the entire patient population. Interestingly post hoc analysis demonstrated improvement in median overall survival in a group of patients with tumors that had high levels of Microsatellite Instability (MSI-H). Irrespective of PDL-1, in patients with MSI-H tumors, median survival was not reached in the pembrolizumab arm *vs.* 8.1 months in the paclitaxel arm [9].

This case demonstrates that all locally advanced and unresectable G/GEJ should be tested for MMR proteins and Microsatellite Stability (MSI) status. Immune checkpoint inhibitor(s) can be extremely effective therapy in metastatic G/GEJ with dMMR as demonstrated previously and in this case and should be the standard of care for this patient population. While this may only be applicable to a small subgroup of patients it represents a therapy with significant improvement in anti-tumor activity compared to conventional chemotherapy.

Additionally, the biopsy specimen in this case demonstrated an improved dynamic immune anti-tumor reaction by the immune system of the patient (host). Cancers develop a variety of mechanisms in order to evade the immune system and are able to suppress the T-cell response which can allow for tumor growth [10]. The immune system has been a target for improving cancer treatment and has included interferons, IL-2, monoclonal antibodies and chimeric antigen receptor cells to name a few. In this patient we are able to see how blocking PD-1 with the monoclonal antibody pembrolizumab led to T cell activation and a robust inflammatory response around this patient's tumor.

Treatment in the metastatic setting is largely determined by weighing the risks of treatment versus benefit of therapy. It is unclear in this setting how long immunotherapy should be continued. Across disease subtypes there are reports of prolonged response after only a short course of immunotherapy [11]. It is suspected that a variety of factors influence optimal duration including disease and patient specific characteristics which are not yet well defined or understood. Additionally, disease assessment has largely been by conventional CT imaging but needs to be evaluated in a different manner than when using conventional chemotherapy due to robust inflammatory response. It will be important to develop diagnostic tests and markers to assess response to allow for tailoring treatment for each patient.

Conclusion

In order to advance the field of cancer treatment we need to continue to identify science-based tumor and patient specific markers that will allow us to better select treatment for each patient. G/GEJ tumors with dMMR or/and MSI-H have a robust response to immunotherapy and these markers should be checked in all patients with locally advanced or metastatic disease.

This case confirms the robust peritumoral inflammatory response and T cell activation caused by PD-1 blockade. As we have additional experience with immunotherapy, we will need to continue to develop tools to determine optimal duration of treatment and response to therapy. Our case demonstrates how using this approach on our young patient had a significant impact on his quality of life and disease outcome.

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