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Case Report

Medullary carcinoma of the duodenum treated with pembrolizumab: a case report

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Background: Medullary carcinoma (MC) is a recognized histologic subtype of colorectal cancer characterized by poor glandular differentiation and intraepithelial lymphocytic infiltrate. However, MC originating from the small intestine is exceedingly rare, with only nine cases described in the literature. Based on previous cases, surgical resection is currently the mainstay of treatment for those with localized disease. We report the first case of a patient who presented with unresectable microsatellite instability-high (MSI-H) MC of the duodenum and was instead treated with pembrolizumab.

Case Description: A 50-year-old man with history of adenocarcinoma of the proximal descending colon status post hemicolectomy and adjuvant treatment with chemotherapy and family history of Lynch syndrome presented with abdominal pain for two weeks. Computed tomography (CT) abdomen/pelvis revealed a 10.7 cm by 4.3 cm mass in the mid-portion of the duodenum abutting against the pancreatic head. Esophagogastroduodenoscopy (EGD) demonstrated circumferential, partially obstructing, intrinsic stenosis of the duodenum with ampullary involvement and likely invasion into the pancreatic head and common bile duct. Endoscopic biopsy of the primary tumor revealed poorly differentiated MC. Immunohistochemical staining showed loss of MLH1 and PMS2 expression. Staging with CT chest showed no evidence of disease. Positron emission tomography (PET) scan redemonstrated circumferential duodenal wall thickening and hypermetabolic activity with standardized uptake value (SUV) max of 26.4, as well as PET-avid epigastric, retroperitoneal, and periaortic lymphadenopathy suggestive of metastasis. He was started on pembrolizumab and found to have stable disease on repeat imaging along with significant improvement in symptoms and performance status.

Conclusions: Due to the rarity of the tumor, there is no standardized approach to treatment. All patients in previously published cases underwent surgical resection. However, our patient was deemed a poor surgical candidate. Given his previous history of colon cancer and treatment with platinum-based therapy, he qualified for pembrolizumab as first line therapy for his MSI-H tumor. To our knowledge, this is the first report of MC of the duodenum as well as the first MC to be treated with pembrolizumab in the first line setting. In order to corroborate the use of immune checkpoint inhibitors as a treatment option for MC of the colon or small intestine, the aggregation of existing and future case data in this unique patient group is certainly warranted.

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Introduction

Medullary carcinoma (MC) is a unique histopathologic subtype of colorectal cancer characterized by a solid growth pattern with poor glandular differentiation and prominent intraepithelial lymphocytic infiltrate (1). A population-based analysis using the Surveillance Epidemiology and End Results (SEER) database found that MCs accounted for 5–8 cases for every 10,000 colon cancers diagnosed (2). However, even more uncommon are cases of MC of the small intestine, with only nine cases described in the literature (3-7). In all of these reported cases, the tumors were located either in the ileum, jejunum, or not specified. Given the rarity of the tumor and limited data available, the best treatment for this patient group remains unclear. For localized tumors, surgical resection appears to be the mainstay of treatment based on previous reports. Here, we report the case of a patient with unresectable microsatellite instability-high (MSI-H) MC of the duodenum treated with pembrolizumab. We present the following case in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-755/rc).

Highlight box

Key findings

- This is the first report of medullary carcinoma of the duodenum as well as the first medullary carcinoma to be treated with pembrolizumab in the first line setting.

What is known and what is new?

- Medullary carcinoma of the small intestine is exceedingly rare. All nine previously reported cases were treated with surgical resection. Our case highlights a potential alternative treatment option in the setting of medullary carcinoma of the small intestine with unresectable disease.

What is the implication, and what should change now?

- Further case data will be needed to determine whether the success from immune checkpoint inhibitors in MSI-H colorectal carcinomas can be translated to the treatment of MC of the colon or small intestine.

Case presentation

A 50-year-old man with history of adenocarcinoma of the proximal descending colon status post hemicolectomy and adjuvant treatment with chemotherapy with capecitabine and oxaliplatin in 2019 presented with abdominal pain and distension for two weeks. He also reported nausea, vomiting, decreased appetite, and constipation with black stools. He had a 10 pack-year smoking history, but no history of alcohol or drug use. Family history was notable for Lynch syndrome in two of his maternal uncles. Physical exam was significant for diffuse abdominal tenderness without any distension, rebound, or guarding. Laboratory evaluation including a complete blood count and comprehensive metabolic panel was remarkable for microcytic anemia with a hemoglobin of 7.3 (13.5–17.5 g/dL). Computed tomography (CT) of the abdomen and pelvis revealed a 10.7 cm by 4.3 cm mass in the mid-portion of the duodenum abutting the pancreatic head (*Figure 1*). Esophagogastroduodenoscopy (EGD) demonstrated circumferential, partially obstructing, intrinsic stenosis of the duodenum with ampullary involvement and likely invasion into the pancreatic head and common bile duct (*Figure 2*). Endoscopic biopsy of the primary tumor demonstrated sheets and nests of malignant cells with extensive tissue necrosis (*Figure 3A,3B*), suggestive of poorly differentiated carcinoma. Immunohistochemical staining was diffusely and strongly positive for pancytokeratin (AE1/AE3) and SATB2. Proliferation index assessed by Ki-67 was 80% by nuclear staining. The malignant cells were negative for CK20, CK7, CDX2, synaptophysin, CD56, calretinin, p63, p40, NKX3.1, TTF-1, Arginase-1, and S100. Of note, there was loss of MLH1 and PMS2 expression. Next-generation sequencing via Omniseq Advance assay determined the tumor as MSI-H with tumor mutation burden of 37.4/Mb and PD-L1 expression of 60% as well as identified a BRCA2 c.6361_6362 deletion mutation. Staging with CT of the chest with contrast showed no evidence of intrathoracic disease. Positron emission tomography (PET) scan redemonstrated circumferential duodenal wall

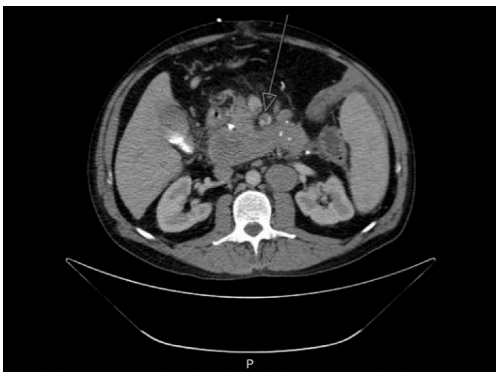

Figure 1 CT abdomen and pelvis with intravenous contrast. Abdominal CT image showing 10.7 cm by 4.3 cm mass (arrow) in the mid-portion of the duodenum that appears to be abutting the pancreatic head. CT, computed tomography.

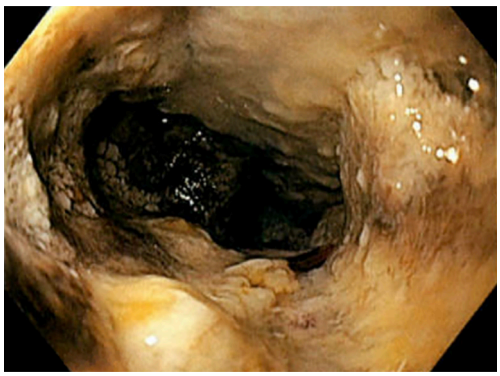

Figure 2 Endoscopic view of ulcerated mass in second portion of the duodenum (D2). Endoscopy revealed a circumferential, partially obstructing, malignant appearing intrinsic stenosis measuring 10 mm in diameter in D2.

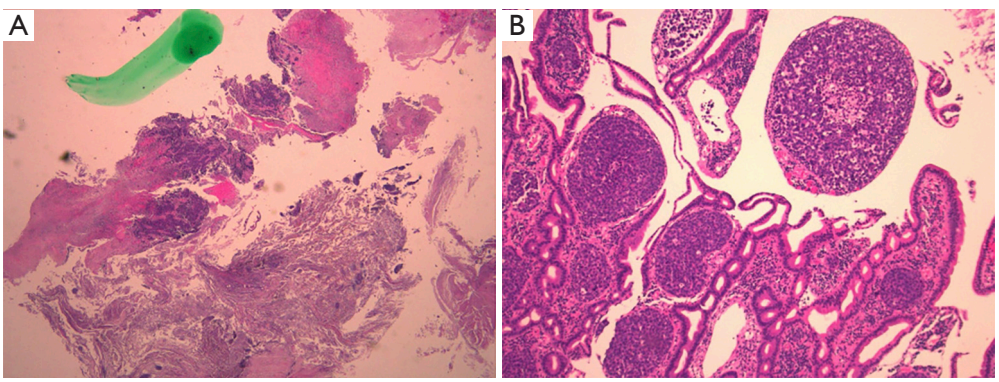

Figure 3 H&E stained slides of biopsy sites of duodenal mass. (A) H&E stain from first duodenal biopsy site, magnification ×10, showing poor glandular differentiation, sheets of infiltrating malignant cells forming trabecular and organoid patterns, and extensive underlying tissue necrosis. (B) H&E stain from second duodenal biopsy site, magnification ×100, showing a fragment of small intestinal type mucosa containing nests of malignant cells. These tumor cells contain pleomorphic nuclei with vesicular chromatin, prominent nucleoli, eosinophilic cytoplasm, and frequent mitotic activity characteristic for medullary carcinoma. H&E, hematoxylin and eosin.

thickening and hypermetabolic activity with an SUVmax of 26.4, as well as PET-avid epigastric, retroperitoneal, and periaortic lymphadenopathy suggestive of metastases (*Figure 4A*,*4B*). BRAFV600E mutation molecular testing was negative. MLH1 promoter methylation testing was positive. Genetic testing was also performed and showed the heterozygous MLH germline c.350C>T mutation. He was started on immunotherapy with pembrolizumab 200 mg every 3 weeks. At cycle 3 of his treatment, his pain had significantly improved, and he continued to tolerate diet and gain weight. He had no immunotherapy-related toxicities. On repeat PET/CT, he was found to have stable disease without worsening of obstruction. Unfortunately, the patient was then lost to follow-up.

Of note, the original pathology of the descending colon revealed poorly differentiated carcinoma with equivocal expression of MLH-1 and partial loss of PMS-2 protein expression. The tumor cells were negative for CK20, CK7, synaptophysin, CD56 but positive for cytokeratin (AE1/AE3) and CDX2.

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was

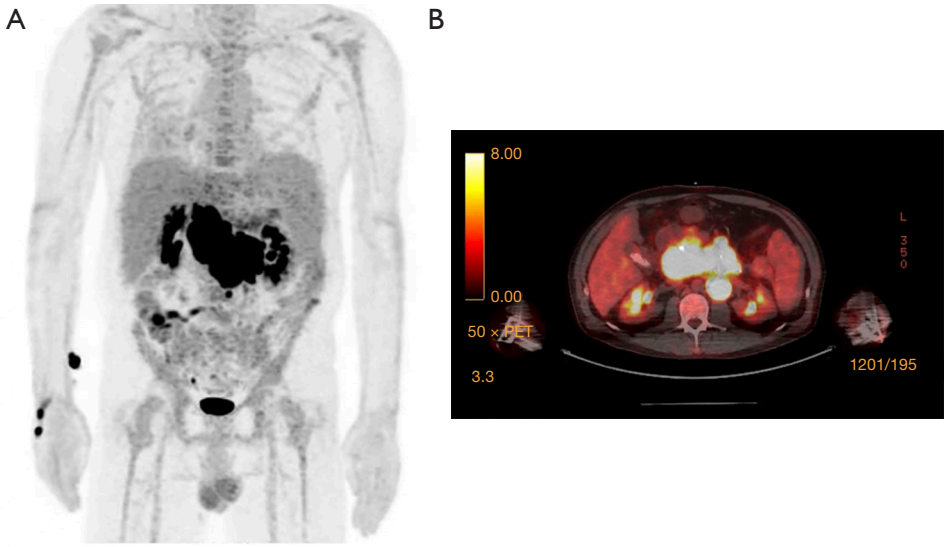

Figure 4 3D MIP PET and axial fused PET/CT imaging of duodenal mass. (A) 3D MIP PET image of duodenal mass. Whole-body anterior projection image of FDG-PET examination demonstrating FDG uptake in the duodenal wall extending from the 2nd–4th portion of the duodenum. (B) Axial fusion image of FDG-PET/CT showing metabolically active lesion of the duodenum with SUV_{max} of 26.4. There is also mild surrounding mesenteric fat stranding and epigastric, retroperitoneal and periaortic lymphadenopathy which are PET-avid suggestive of metastasis. MIP, maximum intensity projection; PET, positron emission tomography; CT, computed tomography; FDG, fluorodeoxyglucose; SUV, standardized uptake value.

obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

MC is a relatively new and distinct histologic subtype of colorectal carcinoma designated by the World Health Organization. It was formerly known as large cell adenocarcinoma with minimal differentiation because of its characteristic sheets of malignant cells with vesicular nuclei, prominent nucleoli, and abundant cytoplasm. However, it is difficult to differentiate MC and poorly differentiated adenocarcinoma based on histology alone since they are morphologically similar. Therefore, immunohistochemical analysis is essential for confirming the diagnosis of MC. The medullary phenotype of colon cancer has been demonstrated to have a strong association with microsatellite instability in at least 60% of cases (8,9). Several studies have sought to characterize the immunohistochemical profile of MC, determining that a significantly higher proportion of MC, as opposed to poorly differentiated colorectal carcinomas, showed loss of staining for mutl homolog1 (MLH-1) and for the intestinal transcription factor CDX2 (9-11). In addition, calretinin staining has been found to be strongly positive in 73% of MCs compared to only 12% of poorly differentiated colonic carcinomas (11). It should be noted that calretinin was negative in our patient, which appears to argue against MC. However, the overall morphology and the aberrant immunohistochemical pattern with loss of CDX2 and CK20 as well as the absent expression of the mismatch repair proteins MLH1 and PMS2 were compatible with a medullary subtype (11).

MC of the small intestine is an exceedingly rare diagnosis. Only nine other cases have been reported in the medical literature (3-7). The tumors were located in the jejunum (4,5), ileum (6,7), or in an unspecified part of the small intestine (3). All but two of these cases were MSI-H, consistent with our patient. Interestingly, the first reported case of MC of the small intestine by Peycru *et al.* was found to be microsatellite stable (7). The MSI status of the other patient (6) was not specified. Compared to MC of the colon, it is difficult to determine the prognosis of this disease as most of these cases lack information regarding follow-up. Of the cases with follow-up data reported, one patient remained disease-free 6 years after resection (5), one patient remained disease-free at 1 year after resection (6), and one patient remained disease-free at an unspecified follow-up date (4).

We contribute the first case of MC of the small intestine located in the duodenum as well as the first MC to be treated with immunotherapy. Considering that colorectal metastasis can morphologically mimic a primary small intestinal or upper gastrointestinal carcinoma, we sought to exclude the possibility of metastatic colon cancer. Original pathology from the descending colon was compared with the pathology from the duodenum, revealing the discordance of CDX2 expression between the two tumors and suggesting our patient's lesion to more likely represent a primary duodenal carcinoma rather than metastatic recurrence of his previous colorectal carcinoma. BRAF molecular testing and MLH1 hypermethylation testing were pursued to distinguish between a germline mutation and somatic inactivation of MLH1. Given the patient's family history of Lynch syndrome, genetic testing for a germline MLH1 mutation was also performed, which indeed revealed a heterozygous MLH germline c.350C>T mutation. Interestingly, the patient's tumor tested negative for the $BRAF_{V600E}$ mutation however tested positive for MLH1 promoter hypermethylation, suggesting a sporadic mutation. Although Lynch Syndrome is characterized by abnormal IHC for MMR proteins and microsatellite instability, it is certainly possible that this patient with Lynch Syndrome had developed a sporadic duodenal tumor due to abnormal methylation of the MLH1 gene promoter.

MC is a rare histologic tumor with no standard treatment. However, consistent with other tumors of the gastrointestinal tract, surgical resection appears to be the mainstay of treatment for those with localized disease in which the role of adjuvant systemic therapy is unclear (3-7). Our patient's case was discussed at our institution's multidisciplinary meeting, and he was deemed not a candidate for surgical resection in the setting of PET-avid epigastric, retroperitoneal, and periaortic lymphadenopathy suggestive of metastases. In the metastatic disease setting, given the majority of the cases are MSI-H and extrapolating from KEYNOTE-177, single agent pembrolizumab might be an appropriate option as first line for these tumors (12). In addition, this tumor was found to be TMB-high, which further supported the choice of pembrolizumab as a viable treatment option with better tolerability compared to cytotoxic regimens (13). However, treatment duration was relatively short, and PET/CT only showed stable disease after three cycles of pembrolizumab. As KEYNOTE-177 demonstrated a median time to response of 2.2 months with pembrolizumab, it remains to be seen whether the magnitude of benefit from immune checkpoint inhibitors in MSI-H MC is similar to that of MSI-H colorectal cancers.

An important limitation of this case report is the lack of data available following the patient's treatment with pembrolizumab. Although he demonstrated improvement in his symptoms and stable disease on PET/CT, we acknowledge that it is difficult to evaluate continued clinical or imaging response to immunotherapy as he was lost to follow up. It should also be noted that the gold standard for the classification of MC is via resection of the tumor. However, in our case, histological diagnosis was confirmed using core biopsy alone based on distinct microscopic and immunohistochemical characteristics.

Conclusions

To our knowledge, this is the first case of duodenal MC as well as the first report of MC to be treated with pembrolizumab in the first line setting. Given the rarity of the condition, specific management guidelines have yet to be established. In the last decade, immune checkpoint inhibitors have been demonstrated to provide durable clinical response, excellent tolerability, and in some cases, even cure in a wide range of tumor types. It remains to be seen whether the benefits of immunotherapy can be translated to the treatment of MC of the colon or small intestine. Further investigations are certainly warranted in this unique population.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-755/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.

com/article/view/10.21037/jgo-22-755/coif). FD has disclosed receiving research grants from AstraZeneca, Bristol-Myers Squibb, Merck, Genentech/Roche, Taiho, Exelixis, Trishula, Leap Therapeutics; receiving consultancy honorarium from Natera, QED, Eisai, Exelixis, Genentech/Roche; and receiving speaker honorarium from Amgen, Eisai, Ipsen, Exelixis, Sirtex, Deciphera, Ipsen, and Natera. May Cho has disclosed receiving honorarium from Amgen, Incyte, Eisai, Ipsen, Astellas, Taiho, Exelixis, QED, I-Mab, Tempus, Seagen, HelioDx, Bayer, AstraZeneca, Genentech/Roche, Pfizer, Natera, Taiho, BMS, Basilea, DSI, and Helsinn. The other 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 the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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