

Medullary Carcinoma of the Colon: A Case Series and Review of the Literature

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Abstract. *Background: Most colon cancers are adenocarcinoma of the colon, which present with a typical histological type. However, a relatively newly-recognized subtype, called medullary carcinoma of the colon, has been characterized. This type is generally divided into subtypes of poorly-differentiated and undifferentiated medullary carcinoma. Only a handful of studies have been conducted thus far, mostly focusing on immunohistochemical and clinical characteristics of the disease. Patients and Methods: Herein we present two cases seen at our hospital within one academic year. The first is the case of a 79-year-old African-American woman, who presented with generalized weakness and gait unsteadiness ultimately diagnosed with a Stage IIIB medullary carcinoma of the proximal colon at the time of surgery, but later found to have metastases to a single paraesophageal lymph node. The second is a case of a 79-year-old Caucasian woman, who presented with several weeks of malaise, nausea, and diarrhea leading to diagnosis of a stage IIB medullary colon carcinoma now receiving chemotherapy. Conclusion: Although these tumors tend to be right-sided and therefore present at an advanced stage, distant metastasis is rare at presentation and is primarily to the liver or regional lymph nodes. Only one study has been performed regarding short-term outcomes, which failed to reach statistical significance, but trended towards better prognosis compared to poorly-differentiated and undifferentiated colonic adenocarcinomas.*

Adenocarcinoma of the colon is a relatively common and well-recognized entity, and is the third most-common type of cancer worldwide, accounting for 9% of cancer incidence.

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Key Words: Medullary carcinoma of the colon, chemotherapy, colon cancer.

In the United States, it was the second leading cause of death from cancer in 2007 (1). In 2010, according to published SEER database statistics, the incidence in the United States was 40.58 cases per 100,000 individuals (2). Prognosis is relatively good depending on stage at presentation, with overall 5-year survival rates being 64.9%. The most common type of colorectal cancer is adenocarcinoma. However, more recently a new histological subtype has been identified, a predominantly solid tumor with little-to-no glandular differentiation, designated as medullary carcinoma of the colon. Overall, this tumor type is believed to carry a relatively favorable prognosis compared with poorly-differentiated or undifferentiated adenocarcinoma of the colon. We present a case of medullary carcinoma of the right colon with rapid progression of disease after a complicated treatment course.

Patients and Methods

Case 1. A 79-year-old female presented to her primary care provider's office with weakness, and the gradual onset of gait unsteadiness. At that time she denied orthostatic light-headedness or vertigo, and she was otherwise asymptomatic with the exception of new intermittent right lower quadrant abdominal pain for a period of months. She denied hematochezia or melena, and was having regular bowel movements. It was also noted that the patient had had an 11-kg weight loss over the prior year, which she attributed to decreased appetite, but had not sought medical attention for. The patient's past medical history was significant for hypertension, hyperlipidemia, aortic stenosis, and a history of Grave's disease. However, it was also noted that she had had a history of several polyps in the ascending, transverse, and sigmoid colon found on screening colonoscopy at age 68, which were removed with cold forceps. The largest being a sessile 6 mm ascending colonic polyp treated with cautery. Pathology of the remaining polyps showed colonic mucosa and hyperplastic polyps. Due to sub-optimal colonic preparations in some areas limiting visualization, repeat colonoscopy after 1 year was recommended but the patient was lost to follow-up until some years later. She had a family history of diabetes, but no known cancers.

At the time of presentation, serum chemistries and a complete blood count were checked and were significant for acute renal insufficiency and a new microcytic anemia with hematocrit of 26%, down from a baseline of 38%. Iron studies were consistent with iron

deficiency anemia. Tests of vitamin B12, folate, thyroid function, liver function, and creatinine kinase were otherwise within normal limits. She was admitted to the hospital for further work-up and management. CT scan of the abdomen and pelvis identified a circumferential colonic thickening of the ascending colon with adjacent fat-stranding and soft tissue nodules. No other lymphadenopathy was noted. Colonoscopy performed during this admission revealed a 6-cm long nearly circumferential lesion at the hepatic flexure. Pathology of the biopsies showed a high-grade poorly-differentiated adenocarcinoma with positive CDX-2, rare positive CK-7, and negative CK20, synaptophysin, and chromogranin on tumor profiling. Follow-up MRI of the abdomen and pelvis showed no evidence of distant disease. Exploratory laparotomy with right hemi-colectomy and adhesion lysis was performed with curative intent. Pathology again showed a high-grade undifferentiated carcinoma consistent with medullary type with intratumoral and peritumoral lymphocytic response, without invasion of the serosal surface. Surgical margins were clear. The tumor had lymphovascular invasion with two out of 18 positive lymph nodes. Staining showed KRAS wildtype and loss of mismatch repair proteins (MLH1 and PMS2). Her tumor was initially staged T3N1Mx (IIb).

Follow-up included serial CEAs, which remained negative. However, on post-operative and pre-adjuvant therapy CT-PET scan, a suspicious peri-esophageal area of increased FDG uptake was noted, as well as an additional area adjacent to the Aorta. The patient underwent fine-needle aspiration biopsy of the peri-esophageal lesion showing metastatic adenocarcinoma consistent with her known colonic primary. Her tumor was therefore up-staged to stage IV with a single distant metastasis to the periesophageal lymph node.

At this point, 12 weeks after diagnosis of her right-sided medullary carcinoma of the colon by colonoscopy, she was initiated on oxaliplatin-xeloda as adjuvant chemotherapy. Her treatment course was complicated by an acute transaminitis developing after the first cycle. Chemotherapy was then held. Abdominal ultrasound showed gallbladder sludge, and was otherwise unremarkable. Hepatitis panel was negative, but her AST, ALT and bilirubin continued to trend upwards. HIDA scan was suggestive of cholestasis, with complete radiotracer uptake but no biliary excretion. MRI and MRCP were negative for parenchymal or biliary lesions. Given the negative work-up, and in consultation with the Hepatology division, her liver function abnormalities were felt to be attributed to her chemotherapy. Liver biopsy was performed and was negative for diffuse infiltrative spread of her cancer, showing drug-induced cholestasis.

She was treated with a course of prednisone, as well as ursodiol and hydroxyzine, but despite this intervention, after an initial improvement her liver enzymes began to rise once more. She represented to the Emergency Department 20 weeks after her initial diagnosis, after developing non-bloody bilious vomiting and several days of non-bloody diarrhea. Physical examination and laboratory data were consistent with a worsening cholestatic picture and acute kidney injury. There were no signs or symptoms of an infectious process. A repeat abdominal ultrasound was performed, and at this time was significant for two pancreatic masses not seen on prior CT scan 12 weeks earlier, measuring 5×3×4 cm inferior to the pancreatic body and 2 cm in diameter between the aorta and inferior vena cava near the pancreatic head. These lesions were confirmed by magnetic resonance abdominal/pelvic imaging as being larger

and more numerous than before with features consistent with lymph nodes and metastases. After further discussion with the patient and her family, it was decided that further more aggressive treatments were not consistent with her goals of care. She was transitioned to comfort measures only and she passed away at home several days after discharge from the hospital.

Case 2. A second patient presented to her primary care physician at 81 years-of-age with several weeks of malaise and intermittent episodes of nausea, vomiting and diarrhea. She had also experienced significant unexplained weight loss in the 10 months leading up to presentation. She had a history of multiple medical problems, which included atrial fibrillation on Coumadin, history of DVT and PE 2 years prior to presentation treated with anticoagulation and placement of an IVC filter, COPD, OSA, a cholecystectomy, and HITT. Previous routine cancer screenings, including colonoscopy 9 years previously, were negative for suspicious or pre-cancerous lesions. She was a lifelong non-smoker who maintains an active and independent lifestyle. She had no known past medical history. Physical examination was unremarkable, except for being notable for an ill-appearing elderly woman. On laboratory work-up, however, she was noted to have an acute microcytic anemia, iron deficiency, and guaiac-positive stools. She was admitted to the hospital for supportive care and work-up. CT abdomen was notable for a lobulated soft tissue thickening of the distal transverse colon and splenic flexure and several liver lesions. Colonoscopy at this time found multiple small-to-medium sized sessile polyps and a medium-sized fungating, friable mass occupying 75-99% of the circumference of the colon causing severe obstruction. Pathology of cold-forceps biopsies showed a poorly-differentiated carcinoma. During the initial hospitalization, the patient also received treatment for a urinary tract infection, atrial fibrillation with rapid ventricular rate, and intravenous fluids, with improvement of her symptoms. Her cardiac medication regimen was also optimized during this time, in anticipation of surgery.

The patient underwent an exploratory laparoscopy with extended right hemicolectomy and partial small bowel resection with primary ileo-to-descending colonic anastomosis, and resection of anterior abdominal wall. She tolerated this surgery well without significant complications. Pathology revealed a large medullary carcinoma with high-grade histology with microsatellite instability and loss of MLH-1 and PMS-2. The tumor was staged as pT4N0Mx or stage IIB. Post-operative PET scan with CT of the chest, abdomen, and pelvis showed only post-operative changes, likely-cystic changes in the liver, and radiotracer activity only associated with small bowel loops adjacent to her suture lines. The patient was initiated on capecitabine and oxaliplatin, which she tolerated well through the first six cycles. Her only complication was chemotherapy-induced neutropenia treated with pegfilgrastim with each cycle. At the time of this article, the patient has no known recurrence of disease.

Discussion

Medullary carcinomas are rare tumors. In one study utilizing the Surveillance Epidemiology and End Results (SEER) database, marking all cases of medullary carcinoma between 1973 and 2006, it was observed that medullary carcinomas represented 5-8 cases for every 10,000 colon cancers diagnosed (3). The mean annual incidence, in the present

study, was 3.47 per 10 million individuals in the population. Incidence increased with age with mean age at-diagnosis being 69.3 ± 12.5 years, with women being diagnosed on average later than men, 72.1 ± 11.2 years *versus* 64.3 ± 13.3 years, respectively. There was a significant female-to-male predominance of 2:1. This subtype of colon cancer is also extraordinarily rare in African-Americans.

Medullary carcinoma of the colon is a relatively new histological type of adenocarcinoma characterized by a solid growth pattern with poorly-differentiated or undifferentiated, predominantly non-glandular, sheets of uniform-type malignant cells with associated intraepithelial lymphocytic infiltrate (3-7). A small number of studies examining immunohistochemical characteristics of this tumor have shown it can be differentiated from poorly-differentiated and undifferentiated colon adenocarcinomas by microsatellite instability, loss of staining for MLH-1 and the intestinal transcription factor CDX2 (4-6). There is also a strongly-positive calretinin staining compared to other poorly-differentiated colonic adenocarcinomas. Tumors also demonstrated diploidy. CEA levels may be high, in one small study 40% of cases, prior to initial treatment (3). Endocrine markers are negative.

These tumors also demonstrated unique clinical characteristics in addition to the demographic and microscopic characteristics described above. Medullary carcinomas tend to present in older females, but at an earlier stage (3). This particular type of colon cancer was most commonly found in the proximal colon, with the next most common sites being the transverse and sigmoid colon. The majority were graded as poorly-differentiated or undifferentiated. Most likely in part due to their frequency in being located in the right colon, tumors tended to present with a larger size. Median tumor size was 7 cm in the Thirunavukarasu *et al.* study (3). In the same study, it was noted that tumor size at presentation was consistent with T3 tumors and without nodal involvement in the majority of cases, and therefore mostly being Stage IIA. Metastasis is rare for this disease. In the handful of studies and single case series available for review, local invasion, regional lymph node metastases, and rarely liver metastases have been described (3, 5, 7). Only 10% of the patients with this tumor type were found to have distant metastasis at the time of diagnosis.

The diagnosis of medullary carcinoma of the colon includes clinical features of a lower gastrointestinal tumor, imaging or direct visualization, elevated tumor markers, and histologic confirmation of diagnosis (3-7). The diagnostic differential of these large right-sided colonic tumors includes neuroendocrine tumors of the colon, poorly-differentiated adenocarcinoma, undifferentiated adenocarcinoma, and sarcoma. Ultimately, the distinction between medullary carcinoma of the colon and other malignancies is performed *via* microscopy and special staining for markers. Medullary

carcinoma of the colon, despite similar histology to neuroendocrine tumors, maintains intestinal differentiation to a point, frequently staining positive for MUC-1, MUC-2, and TFF-2 (6). While undifferentiated adenocarcinoma and colonic medullary carcinoma may be difficult to identify by microscopy alone, medullary carcinomas can be differentiated by strong calretinin staining and loss of MLH-1 and CDX2 staining in the majority of cases. In one study it was also noted that there was more commonly a lack of stabilization of the p53 protein and microsatellite instability was almost completely limited to poorly-differentiated adenocarcinoma of the medullary type (4).

In comparison to undifferentiated and poorly-differentiated adenocarcinomas of the colon, medullary carcinomas are believed to have a relatively favorable prognosis (3-5). In the study of Thirunavukarasu *et al.*, where 50 cases of medullary carcinoma of the colon were identified from the SEER database between 2004-2006, the overall survival was 92.7% at 1-year and 73.8% at 2-years, as compared with 70.5% and 58.4% for poorly-differentiated adenocarcinoma respectively and 69.9% and 53.1% for undifferentiated tumors (3). It is important to note, however, that in the study by Thirunavukarasu *et al.*, no statistically significantly increased survival was noted between medullary carcinoma and the other types, likely due to small sample size, though there was a trend towards improved survival in medullary carcinoma. Conclusions about outcomes are limited regarding early survival given the recent recognition of this distinct tumor type in studies. Among medullary carcinomas, interestingly, undifferentiated medullary carcinoma compared to poorly-differentiated medullary carcinomas also appeared to have a trend towards worse survival.

Likely in part due to the rarity of the tumor, treatment strategies in medullary carcinoma *versus* high-grade adenocarcinomas have not been compared to date. In the study by Thirunavukarasu *et al.*, all patients with medullary carcinoma had undergone surgery (3). In Jessurun *et al.*, all 11 patients studied in the case series had undergone right hemicolectomy or total colectomy (7). To our knowledge, chemotherapy strategies have not been discussed.

The single case series published to date including 11 patients with medullary carcinoma of the colon is the one of Jessurun, *et al.* (7). The study group comprised of patients prospectively identified at one of five medical Centers in North America. All patients presented after noticing blood in their stools, plus abdominal symptoms such as pain, diarrhea, or changes in bowel habits. Only one patient had a palpable mass on the right side of her abdomen. All patients were female and the ages of the patients at diagnosis ranged from 26 to 92 years of age. Tumors were large bulky masses with an expansive growth pattern located in the cecum in 8 patients, right colon in two patients, and both the cecum and sigmoid colons in one patient. Frequently the tumor would

invade the lumen as a sessile polyp with central ulceration, but the majority of the tumor extended extra-luminally and in all cases showed infiltration of the pericolic soft tissues. Eight patients had lymph node metastases and one patient had liver metastasis at the time of presentation. Eight patients underwent right hemi-colectomy and three patients underwent a subtotal colectomy. Pathology of the tumors were consistent with the features described above, with the exception that inclusion criteria in this study only required 80% solid tumor growth patterns. Of these individuals, follow-up information was available for only 8. Two patients had Duke's stage B tumors, and on follow-up were alive and well 2 and 4 years after diagnosis. Six patients had Duke's stage C disease, two of which died in the immediate post-operative period, two are alive and well without known recurrence 14 and 25 months post-operatively, one survived with asymptomatic liver metastases 4 years after the original presentation, and one patient died of tumor recurrence and metastases 1 year after resection.

The patient with liver tumor metastasis is an interesting case and perhaps should be regarded as a unique case that should perhaps be taken separately from the others. She was 41 years at the time of diagnosis. Her primary tumor showed areas typical for mucinous adenocarcinoma, though it is unclear at what percentage of the tumor exactly. The liver lesions were also resected, which interestingly showed histology consistent with mucinous adenocarcinoma with only a small component of "medullary adenocarcinoma of the colon". Follow-up information is not available for this patient.

Our patients, being both women diagnosed at age 79, fit the typical sex and age demographics for this cancer. However, several factors make the first case described herein, unique among the others described in the literature. This tumor type is exceedingly rare in African-Americans (2). Despite having a diagnosis of a tumor-type believed to have a generally favorable prognosis, the first patient did not tolerate treatment well and experienced rapid disease progression after treatment was held due to medical complications. Her pattern of metastasis to a para-esophageal lymph node, recognized shortly after initial diagnosis and after initial resection, is unique compared to other published cases. Meanwhile, in the second case, the patient has tolerated chemotherapy with capecitabine and oxaliplatin well and has had no known recurrence seven months from her initial diagnosis and surgery. Relatively little is known about prognostic or predictive factors in patients with this tumor type, so we are unable to comment further on this regard.

Medullary carcinoma of the colon is a well-recognized sub-type of colon cancers. It has defined microscopic and immunohistochemical characteristics. In the case reviews currently published, overall prognosis is favorable compared

to poorly-differentiated or undifferentiated adenocarcinomas. However, not many published data are currently available examining treatment strategies and response. One possibility arises that improved survival observed is due to presentation-associated factors, such as the low incidence of metastasis at-diagnosis. With time, a greater number of examined patients may reveal more about the behavior of this illness as well as prognostic factors and expected responses to treatment.

Conflicts of Interest

The Authors state there are no conflicts of interest and have received no payment in preparation of this manuscript.

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Received January 9, 2014

Revised March 14, 2014

Accepted March 17, 2014