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Medullary colonic carcinomas present with early-stage disease and do not express neuroendocrine markers by immunohistochemistry

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Abstract

Background Medullary colonic carcinoma (MCC) is a rare and distinct phenotype of colorectal cancers characterized histologically by sheets of malignant cells with vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm, exhibiting prominent infiltration by lymphocytes and neutrophilic granulocytes. We present the clinicopathologic and immunohistochemical characteristics of this rare tumor in our patient population.

Methods Eleven cases diagnosed with MCC from 1996-2020 met the diagnostic histologic criteria and had tissue blocks available for further analysis. Immunohistochemistry for mismatch repair deficiency, CDX2, synaptophysin, and chromogranin, and microsatellite instability testing by polymerase chain reaction were performed. Additional clinical information was obtained from the electronic medical records.

Results The median age at diagnosis was 69 years. MCC was more common in women (64%) than men (36%) and all (100%) cases involved the right colon. The median carcinoembryonic antigen level at diagnosis was 2.8 ng/mL. Lymphovascular invasion and perineural invasion occurred in 64% and 9% of cases, respectively. Synaptophysin and chromogranin showed no expression in any of the cases (0%), and CDX2 was only expressed in 18% of cases by immunohistochemistry. Most patients (73%) presented with stage II disease and 7 (64%) cases were microsatellite instability-high. Only lymph node metastasis showed an association with overall survival (OS) (hazard ratio 0.04, 95% confidence interval 0.0003-0.78; P=0.035). During a median follow up of 1.25 years, the median OS was not estimable as the survival curve did not reach the median point of survival, indicating that more than half of the patients were still alive at the end of the study.

Conclusion Based on our experience, neuroendocrine markers, including synaptophysin and chromogranin, are not expressed in MCC, and many patients present with early-stage disease.

Keywords Medullary colonic carcinoma, colon cancer, neuroendocrine markers, screening, prognosis

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Conflict of Interest: None

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Introduction

Colorectal cancer (CRC) represents the third most common cancer and the third leading cause of cancer-related death in men and women in the United States [1]. Medullary colonic carcinoma (MCC) is a unique and distinct histologic phenotype that is recognized in the World Health Organization's (WHO) classification of colorectal tumors [2]. At present, the only standard diagnostic guideline is that delineated in the 2019 WHO classification of tumors of the digestive system [2], which states that MCC is composed of "sheets of malignant cells with vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm, exhibiting prominent infiltration by

lymphocytes and neutrophilic granulocytes." In both clinical and research settings, MCC is commonly perceived as a distinct clinicopathological entity with specific prognostic relevance and molecular pathogenesis [1]. Previous studies have suggested that tumors with medullary histology are strongly associated with DNA mismatch repair (MMR) deficiency, despite their "poorly differentiated" histologic appearance [1]. Similarly, the American Joint Committee on Cancer (AJCC) currently recognizes MCC as a distinct histologic subtype of CRC [3].

What appears to be underrecognized, however, is that the morphological diagnosis of MCC can be challenging and the clinical outcome of these tumors can be variable [4]. For diagnosis, the study by Lee *et al* shows that a wide spectrum of "medullary" morphology exists in CRCs, and there are frequent intermediate forms between classic MCC and conventional poorly differentiated carcinoma [1]. This observation is further complicated by the fact that the existing WHO definition has not been standardized. Additionally, due to its poorly differentiated phenotype, several differential diagnoses, including neuroendocrine carcinomas, may be considered.

Of the histologic variants of CRC, MCC is a rare phenotype with a reported rate of 0.5-9 cases per 1000 [5]. Previous studies have shown that patients with MCC are frequently elderly women, and the most common location is the cecum or the ascending colon [5]. The tumor has an expansive growth pattern and is most often diagnosed at an advanced stage (T3 or T4). Additionally, it is reported that fewer patients present with lymph node metastases at the time of diagnosis (5). We therefore aimed to study the clinicopathologic and immunohistochemical (IHC) characteristics of this rare disease within our patient population.

Patients and methods

This was a retrospective study conducted at the Department of Pathology of the Wayne State University School of Medicine/ Detroit Medical Center in Michigan. Institutional review board (IRB) approval was obtained from the Wayne State University IRB (IRB-20-05-2248). We reviewed MCC cases from January 1996 to July 2020 at our institution. We conducted our search using the following search terms: "medullary colonic carcinoma", "medullary carcinoma of the colon", "poorly differentiated cancer of the colon", "undifferentiated colonic carcinoma", and "medullary colon carcinoma." Two surgical pathologists (EA and RB, a gastrointestinal pathologist), reviewed clinicopathologic records, including hematoxylin and eosin-stained slides, to confirm a diagnosis of MCC. Morphologic features that characterize MCC include a syncytial growth pattern, large vesicular nuclei with conspicuous nucleoli and a prominent intratumoral lymphocytic infiltrate [6-8]. Tumors were accepted as MCC if they showed the characteristic histologic features that currently define this tumor, as previously stated [2]. Cases were excluded if they lacked characteristic syncytial tumor morphology with a prominent intratumoral lymphocytic infiltrate, or showed morphology more typical of poorly differentiated adenocarcinoma, characterized by more pleomorphic morphology with some evidence of glandular differentiation [9]. MMR deficiency by IHC for MLH1 (monoclonal; clone: ES05; Dako Corporation, Carpinteria, CA), MSH2 (monoclonal; clone: FE11; Dako Corporation, Carpinteria, CA), MSH6 (Rabbit monoclonal; clone: EP49; Dako Corporation, Carpinteria, CA), PMS2 (Rabbit monoclonal; clone: EP51; Dako Corporation, Carpinteria, CA) proteins and microsatellite instability-high (MSI-H) status by polymerase chain reaction (PCR-ABI 3130xL Platform) were performed on available tissue blocks. Since neuroendocrine carcinoma was the top differential diagnosis in our patient population, additional IHCs, including synaptophysin (monoclonal; clone: DAK-SYNAP; Dako Corporation, Carpinteria, CA), chromogranin A (monoclonal; clone: DAK-A3; Dako Corporation, Carpinteria, CA) and CDX2 (monoclonal; clone: DAK-CDX2; Dako Corporation, Carpinteria, CA), were also performed on available tissue blocks. Tissue sections were subjected to routine processing and embedding after fixation in 10% buffered formalin. Four-μm sections were obtained and stained with hematoxylin and eosin stain. Adequate positive and negative controls were employed throughout. IHC labeling for CDX2, synaptophysin and chromogranin was scored using previously reported criteria [10,11]. Additional clinicopathologic information, including demography, tumor size, the portion of colon involved, metastatic disease, AJCC stage (8th edition), comorbidity (obesity/overweight, diabetes, hypertension, smoking), treatment received, carcinoembryonic antigen (CEA) levels and overall survival (OS), defined as the time from diagnosis to last follow-up or death, were obtained from the electronic medical records.

Statistical analysis

Patient baseline characteristics were summarized by median (range) and frequency (percentage) for continuous and categorical variables, respectively. The distribution of OS was described graphically using a Kaplan-Meier (KM) curve. The median follow-up time was estimated using the reverse KM method. In view of the small sample size, Cox proportional regression analyses were limited to univariable analyses. Firth's Cox regression models were used to reduce bias in maximum likelihood estimation caused by rare events.

Results

Following our review, 27 cases diagnosed as MCC were identified. However, only 11 cases met the WHO's diagnostic

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definition of MCC (2) and had available tissue blocks for further analysis (Fig. 1A,B). The clinicopathologic characteristics of the cases are presented in Table 1. The median age at diagnosis was 69 (range 59-91) years. Six (55%) patients were Caucasians, 4 (36%) were Black/African Americans (AA), and 1 (9%) belonged to other ethnicities. MCC was more common in women (7; 64%) than men (4; 36%). The median tumor size was 8.1 (range 4.6-14) cm, and all cases of MCC (100%) occurred in the right colon. All tumors were poorly differentiated (100%). The median CEA level at diagnosis was 2.8 (range 0.2-6.5) ng/mL. Seven (64%) cases had lymphovascular invasion and both lymph node metastasis and perineural invasion were present in 1 (9%) case. Precursor lesions (tubular/villous adenoma) were present in 2 (18%) cases. Positive tumor margins were observed in 2 (18%) cases. Metastatic disease was observed in 2 cases and those metastases were to the abdominal wall (50%) and scapula (50%). Most patients (8; 73%) presented with stage II tumors. One (9%) patient presented with stage III disease and 2 (18%) patients presented with stage IV disease. Seven of the 11 (64%) cases showed loss of nuclear expression of MMR proteins (MLH1 and PMS2) by IHC. All 7 cases with MMR loss also exhibited MLH1 promoter hypermethylation and BRAF V600E mutations. All 7 cases were also MSI-H by PCR. IHC showed a lack of immunoreactivity with synaptophysin and chromogranin in all 11 tissue blocks tested. Additionally, CDX2 was only focally expressed in 2 (18%) cases (Fig. 2A,B). Two (18%) patients were obese/overweight (body mass index ≥25 kg/m^2), 5 (45%) had diabetes, 9 (82%) were hypertensive, and 4 (36%) were smokers. All patients had surgical resections of their primary tumors; however, 3 (27%) patients received additional chemotherapy.

Univariable Firth's Cox proportional hazard regression analysis of several clinicopathologic characteristics with OS showed that only metastatic disease to the lymph node was associated with OS (hazard ratio 0.04, 95% confidence interval [CI] 0.0003-0.78; P=0.035). None of the variables examined, including stage, lymphovascular invasion, tumor size, perineural invasion, precursor lesions, positive margins, age at diagnosis, race, sex, being obese/overweight, diabetes, hypertension, smoking status, chemotherapy, CEA levels at diagnosis, CDX2 expression and MSI status, had any impact on OS (Table 2). During a median follow up of 1.25 years

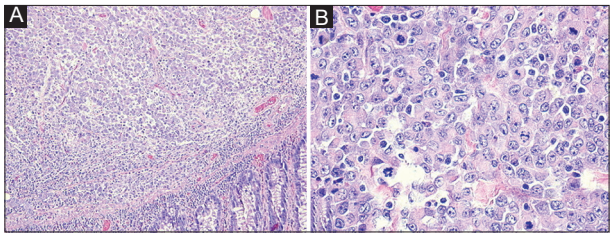

Figure 1 Composite hematoxylin and eosin image. A: Colonic tumor showing a solid growth pattern with a pushing border and conspicuous intratumoral and peritumoral lymphocytes. Normal colonic mucosa can be seen in the lower right of the image- 4× magnification. B: Higher magnification (40×) of the tumor in A, showing a poorly differentiated tumor with syncytial morphology, abundant eosinophilic cytoplasm, prominent mitotic figures and intratumoral lymphocytes

Table 1 Patient clinicopathologic characteristics

Patient characteristics	N=11
Age at diagnosis - median (range)	69 (59,91)
Race - no. (%)	
White	6 (55)
Black/African American	4 (36)
Other	1 (9)
Sex - no. (%)	
Female	7 (64)
Male	4 (36)
Tumor size (cm) - median (range)	8.1 (4.6-14)
Portion of colon - no. (%)	
Right colon	11 (100)
Tumor grade - no. (%)	
Poor	11 (100)
Lymphovascular invasion - no. (%)	
Yes	7 (64)
No	4 (36)
Lymph node metastases - no. (%)	
Yes	1 (9)
No	10 (91)
Perineural invasion - no. (%)	
Yes	1 (9)
No	10 (91)
Precursor lesion - no. (%)	
None	9 (82)
Tubular/villous adenoma	2 (18)
Margins - no. (%)	
Positive	2 (18)
Negative	9 (82)
Stage - no. (%)	
II	8 (73)
III	1 (9)
IV	2 (18)
Obesity/overweight - no. (%)	
Yes	2 (18)
No	9 (82)
Diabetes - no. (%)	
Yes	5 (45)
No	6 (55)
Hypertension - no. (%)	
Yes	9 (82)
No	2 (18)
Smoking - no. (%)	
Yes	4 (36)
No	7 (64)
Surgery - no. (%)	
Yes	11 (100)
Chemotherapy - no. (%)	
Yes	3 (27)
No	8 (73)
Radiotherapy - no. (%)	
No	11 (100)

(Contd...)

Table 1 *(Continued)*

Patient characteristics	N=11
Mismatch repair deficient/microsatellite instability-high - no. (%)	
Yes	7 (64)
No	4 (36)
Carcinoembryonic antigen (diagnosis) - median (range)	2.8 (0.2-6.5)
Synaptophysin - no. (%)	
No	11 (100)
Chromogranin - no. (%)	
No	11 (100)
CDX2 - no. (%)	
Yes	2 (18)
No	9 (82)

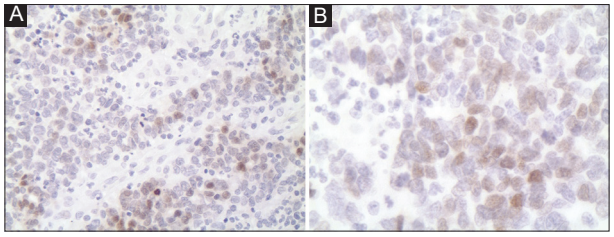

Figure 2 Composite image showing CDX2 immunoreactivity by immunohistochemistry. A: 20× magnification; B: 40× magnification

(95%CI 0.5 - not reached), the median OS was not estimable as the survival curve did not reach the median point of survival, indicating that more than half of the patients were still alive at the end of the study (Fig. 3).

Discussion

MCC is a rare histologic variant of CRC and its diagnosis can be challenging in clinical practice. Currently, only the diagnostic criteria outlined in the current WHO classification of tumors of the digestive system [2] represent the standard of practice, which was applied in the current study. Nonetheless, our study adds to the current body of knowledge and emphasizes the need for standardization of this rare disease. Our experience shows that MCC is more common in elderly patients with a median age of 69 years. MCC is also more common in Caucasian patients (55%) and tends to occur more commonly in women (64%). Our findings are consistent with what has been previously reported in the literature, where MCC was found to be more common in elderly Caucasian women [12]. A unique challenge in diagnosing MCC in clinical practice is the ability to differentiate it from poorly differentiated adenocarcinoma (PDA). Strictly applying the WHO histologic criteria—sheets of malignant cells with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, and prominent infiltration by

Table 2 Univariable Firth Cox proportional hazard regression analysis of overall survival

Patient characteristics	Event/n	HR (95%CI)	P-value
Age at diagnosis	1/11	1.18 (0.98-1.84)	0.075
Race			
White	0/6	Ref.	
Non-white	1/5	2.40 (0.13-350.21)	0.569
Sex			
Female	1/7	Ref.	
Male	0/4	0.42 (0.003-7.81)	0.569
Tumor size (cm)	1/11	1.07 (0.56-1.91)	0.793
Lymphovascular invasion			
Yes	1/7	Ref.	
No	0/4	1.17 (0.01-21.87)	0.926
Lymph node metastases			
Yes	1/1	Ref.	
No	0/10	0.04 0.0003-0.78)	0.035
Perineural invasion			
Yes	0/1	Ref.	
No	1/10	0.37 (0.02-54.72)	0.583
Precursor lesion			
None	0/9	Ref.	
Tubular/villous adenoma	1/2	10.50 (0.56-1532.16)	0.113
Margins			
Positive	0/2	Ref.	
Negative	1/9	0.86 (0.05-125.07)	0.926
Stage			
II	0/8	Ref.	
III-IV	1/3	6.00 (0.32-875.52)	0.228
Obesity/overweight			
Yes	0/2	Ref.	
No	1/9	0.86 (0.05-125.07)	0.926
Diabetes			
Yes	0/5	Ref.	
No	1/6	2.40 (0.13-350.21)	0.569
Hypertension			
Yes	1/9	Ref.	
No	0/2	1.17 (0.01-21.87)	0.926
Smoking			
Yes	1/4	Ref.	
No	0/7	0.27 (0.002-5.00)	0.380

(Contd...)

Table 2 *(Continued)*

Patient characteristics	Event/n	HR (95%CI)	P-value
Chemotherapy			
Yes	0/3	Ref.	
No	1/8	1.50 (0.08-218.88)	0.798
Mismatch repair deficient/ microsatellite instability-high			
Yes	1/7	Ref.	
No	0/4	1.17 (0.01-21.87)	0.926
Carcinoembryonic antigen (diagnosis)	1/11	0.39 (0.0001-1.45)	0.195
CDX2			
Yes	0/2	Ref.	
No	1/9	0.86 (0.05-125.07)	0.926

Event/n, number of events and patients; HR, hazard ratio; CI, confidence interval

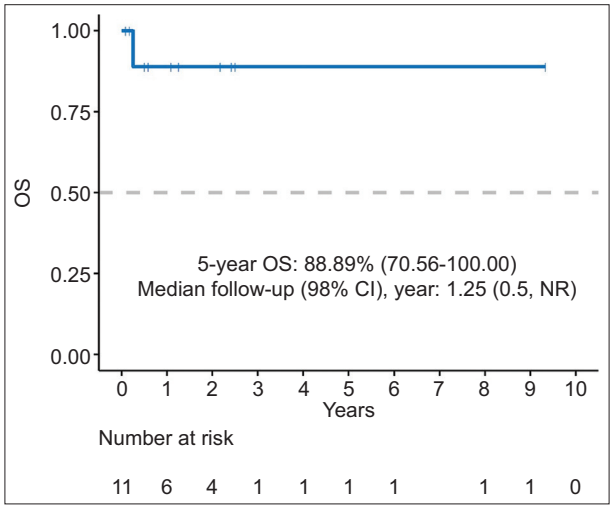

Figure 3 Kaplan-Meier (KM) curve of overall survival (OS). The median follow-up was calculated using the reverse KM method. *CI, confidence interval; NR, not reached*

intratumoral lymphocytes [2]—may help differentiate MCC from PDA, whose histologic features are more variable. A diagnosis of MCC is most likely to be favored if at least a part of the tumor shows characteristic morphology, especially with associated prominent tumor-infiltrating lymphocytes. The potential for a missed diagnosis of this rare tumor entity emphasizes the need for the development of more uniform and stricter criteria in diagnosing MCC in CRC patients. In terms of specific histologic findings, lymphovascular invasion occurred more frequently (64%) than lymph node metastasis (9%) and perineural invasion (9%) in this series. Our findings are consistent with what has been previously reported in other studies [14,15], and emphasize a unique characteristic of this colorectal tumor variant: MCC is different from conventional CRC, which typically shows more lymph node metastases and perineural invasiveness. Most (73%) of our patients presented at a low clinical stage (stage II). Other investigators found that most of their patients presented with stage III and IV disease [15]. We found one previous study that reported almost equal representation between early stage (stages I and II) and late stage (stages III and IV) disease [14]. However, some other studies have shown more cases of MCC presenting with early-stage disease [1,9], which is in line with our experience. A common observation in MCC is that many cases are MMR deficient and/or MSI-H. Of the 11 cases tested in this study, 7 (64%) were MMR deficient (loss of nuclear expression of MLH1 and PMS2) and exhibited MLH1 promoter hypermethylation and BRAF V600E mutations. All 7 (64%) MMR deficient cases were also MSI-H. The MMR deficiency and MSI patterns seen in our study are consistent with what has been previously described [4,13]. Metastatic disease was seen in 2 cases to the abdominal wall and scapula. Other studies have not characterized the sites of distant metastasis in their reports. Neuroendocrine carcinoma was the top differential diagnosis in our patient population, and testing for neuroendocrine differentiation with synaptophysin and chromogranin by IHC was negative. Our findings of negative neuroendocrine immunoreactivity in MCC have been previously documented in another study [16]. Therefore, we suggest that, although MCC and neuroendocrine carcinoma may have overlapping histologic characteristics, a diagnosis of neuroendocrine carcinoma may be less favored based on negative immunoreactivities with neuroendocrine markers.

All patients underwent surgical resection of their tumors. However, 3 (27%) patient(s) received additional chemotherapy as part of their management. Univariable Firth's Cox proportional hazard regression analysis performed on several clinicopathologic characteristics showed that only positive lymph node metastasis is associated with OS. Furthermore, during a median follow up of 1.25 (range 1-5.25) years, the survival curve for OS did not reach the median point, indicating that more than half of the patients were still alive at the end of the study. We therefore emphasize that, regardless of the histologic classification of MCC, preventive cancer care that guarantees access to screening with the use of regular colonoscopies should be promoted for populations to prevent CRC.

Our study is not devoid of limitations. We recognize that its retrospective nature introduces its own inherent biases. However, given that MCC is very rare, accumulating patients in a prospective trial would prove challenging and very difficult. Additionally, given the limited number of patients in our cohort, it is possible that our findings may not be representative of the general population. Nonetheless, despite these obvious limitations, we have been able to describe the clinicopathologic characteristic of this rare tumor within our patient population. We anticipate that results from our study will add to the current body of knowledge of MCC and may lead to the standardization of this rare disease and influence public health campaigns. Furthermore, based on our experience, neuroendocrine markers, including synaptophysin and chromogranin, are not expressed in MCC, while many patients present with early-stage disease.

Summary Box

What is already known:

- Medullary colon cancer is a rare histologic variant of colonic adenocarcinoma
- Prognosis is good despite patients presenting with late-stage disease
- Diagnosis of medullary colonic carcinoma is challenging in clinical practice and can be difficult to differentiate from other diagnostic mimics
- Medullary colonic carcinoma is strongly associated with DNA mismatch repair deficiency

What the new findings are:

- Most patients in this study presented with early-stage disease and their survival curve did not reach the median point of survival, which indicates that more than half of the patients were still alive at the end of the study, suggesting that the clinical presentation of this disease is variable
- Diagnosis of medullary carcinoma is challenging in clinical practice, and other than the current WHO definition for this category of tumors, more standardized and uniform criteria should be developed
- Medullary colonic carcinomas do not express neuroendocrine markers, which is a major differential diagnostic consideration with these tumors

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