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Primary medullary adenocarcinoma of the colon: Literature review and case series

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ABSTRACT

Aims: Medullary carcinoma of the colon is a rare subtype of adenocarcinoma, first described in 1999. Clinically known to have a favorably prognosis in comparison to poorly differentiated cancers, it is invariably associated with mismatch gene repair. This is an observational study of Hobart's patient population with medullary cancer, and compares data with the current literature.

Methods: We performed a search of the pathological database at our institution for medullary adenocarcinomas between the years of 2016 and 2023 and reviewed their clinical information to collect all relevant data including patient history, hospital admissions, surgery and clinic visits. We then performed a literature search using PubMed for search terms medullary cancer/carcinoma of the colon/colorectum.

Results: Eleven patients were found in our database, 34 papers in the literature (19 retrospective cohort studies and 13 case reports). 81.8% (vs. 73.22% in cohort studies) were females. 8/11 patients had lymphovascular invasion (LVI) with 2/11 patients had perineural involvement (PNI). The immunohistochemistry (IHC) results showed that in all (11/11) patients' tumors, there was a loss of MLH1 and PMS2 proteins, while MSH2 and MSH6 proteins were present. Cohort studies demonstrated 302/1897 (15.92%) patients had perineural invasion (PNI) with 1133/2151 (52.67%) demonstrating LVI. MLH1 testing was available for 192 patients, with 93.75% having loss of MLH1.

Conclusion: Our cohort of medullary cancer patients was similar to that in the literature, with regard to demographic, staging, and tumor characteristics. A longer follow-up time is required for our cohort to produce comparable survival outcomes.

Keywords: Colon cancer, Colorectal, Primary medullary colon cancer

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INTRODUCTION

Medullary carcinoma (MCC) of the colon is a recently recognized but rare subtype of colonic adenocarcinoma, with the first published case documented in 1999 [1, 2]. It is not to be conflated with breast and thyroid cancers because the clinicopathological features are quite different [3]. It has a strong association with Lynch syndrome and sporadic causes of mismatch repair (MMR) deficiency, without the usual immunohistochemical (IHC) staining pattern or staining results, seen in colorectal adenocarcinoma [4]. Clinically this subtype is associated with a favorable prognosis when compared to other poorly differentiated/undifferentiated colorectal cancers of a similar grade and is invariably associated with mismatch gene repair deficiency [5, 6]. It has a propensity to affect older women >65 years of age more than men, has a lower risk of lymph node spread and occurs more often on the right side of the colon [4, 7]. Histologically, MCC can be misclassified as poorly differentiated adenocarcinoma not otherwise specified (NOS) [8]. It is typically characterized by sheets of malignant cells with indistinct cell boundaries, vesicular nuclei, prominent nucleoli, abundant eosinophilic cytoplasm, and prominent intra-tumoral lymphocytes and neutrophils. It invariably presents with microsatellite instability [9].

Given MCC is a rare subtype of colorectal cancer (CRC), and there is some literature pertaining to this subtype, we aim to present data from a local Australian perspective and compare it to the current literature.

MATERIALS AND METHODS

A search of the anatomical pathology database at our institution for medullary cancers of the colon between 2016 and 2023 was performed and patients' digital medical record was assessed. Data were extracted on clinical history, operation notes, investigations, and outpatient notes.

For the literature search, search terms "colon," "rectum," "colorectal," "medullary carcinoma," and "solid type poorly differentiated carcinoma" were entered to retrieve relevant articles in the PubMed and MEDLINE databases up to August 2023 using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Titles and abstracts were screened for relevance and exclusion. Original and review articles were searched utilizing the same inclusion/exclusion criteria (Figure 1). The initial search yielded 260 results (Figures 2 and 3). These articles then were filtered by 2 authors, then the 18 abstracts were read, and secondary references searched where indicated. Secondary references were utilized and duplicates were eliminated for a result of 402 articles. After filtering the abstracts according to criteria, 13 articles were then read and included in the study. The combination of the initial search (18 articles), and a search of the references (13 articles) yielded a total of 31 articles—13 case reports and 18 retrospective cohort studies for our literature review. One of the papers in the references was a meta-analysis of medullary cancer of the colon from 2016—the papers that informed this study were included in our final count [5].

Approval for our case series was obtained from the Tasmanian Human Research Ethics Committee (ref. no. 29765).

INCLUSION CRITERIA	EXCLUSION CRITERIA
Primary medullary cancers of the colon	Medullary cancers of other organ origin
Human subjects	Non-human subjects
English articles	Non-English articles
Data on demographics and outcomes	Insufficient data
Research journal articles	Books, Letters, Opinions

Figure 1: Inclusion/exclusion criteria.

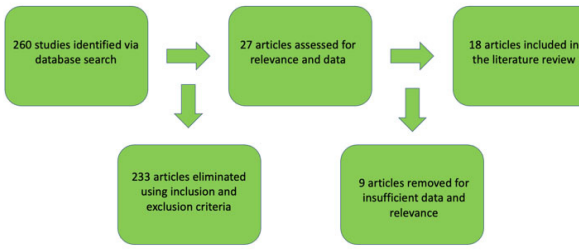

Figure 2: Initial search strategy with elimination boxes utilizing PRISMA guidelines. Secondary references not included in diagram.

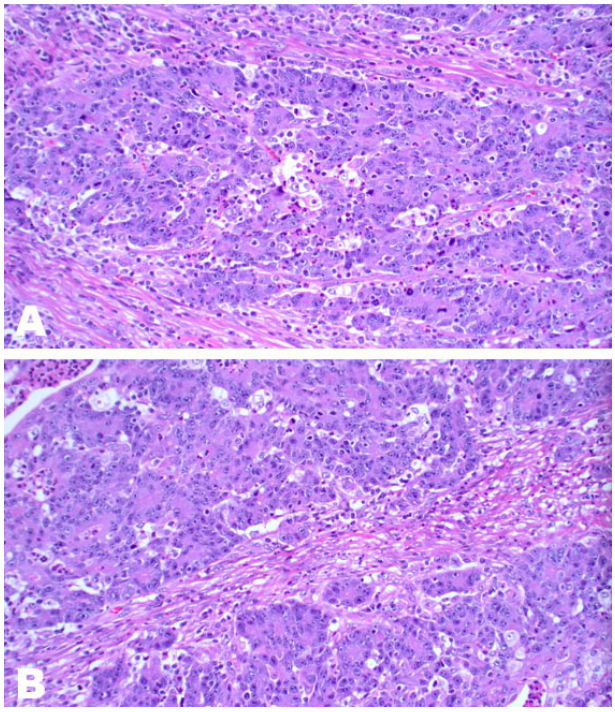

Figure 3: (A) and (B) H&E stained sections at 20× magnification show medullary carcinoma with trabecular and organoid growth pattern. Tumor cells show amphophilic cytoplasm with ovoid nuclei containing vesicular chromatin with prominent nucleoli.

RESULTS

Overall

Eleven patients at the institution had MCC in their pathology over seven years of our database search. We found 18 retrospective cohort studies with a total of 3158 patients, as well as 13 case reports involving MCC of the colon, one of which documented 2 patients.

Age and sex

Nine (81.8%) of the 11 patients in our local database were females with a ratio of 3:1 compared to males; ages of patients ranged from 56 to 93, with a mean age of 75.3 (Table 1). Average age in case reports was 68.5 years. Cohort studies' results had an average age of 70.5 years; 73.2% were females (out of 3144 patients due to clinical data availability).

Comorbidities and presentation

Case series (Table 1)

Four (36.4%) of 11 patients were ex-smokers or obese, with 2 (18.2%) patients having previous primary malignancies—breast and prostate/colon cancer, respectively. The patient with prostate cancer also had a previous history of a colonic adenocarcinoma which was treated with surgery alone. Four (36.4%) patients presented with iron deficiency anemia (IDA) and a positive fecal occult blood test, while 2 (18.2%) patients presented via the Australian National Bowel Screening program (NBSP).

Case reports

Average age of patients was 68.5 years, with MCC predominantly affecting females 10 of 13 (76.9%). Three of 14 (21.4%) patients had ischemic heart disease, and only one patient was an ex-smoker. Two of 11 (18.2%) patients had other primary malignancies—multiple myeloma and melanoma of the chest. Six of 14 (42.9%) patients presented with abdominal pain, and 4 (28.6%) patients had either iron deficiency anemia or per-rectal (PR) bleeding (Table 2).

Cohort studies

Cohort studies had a sample of 3144 patients, with 2302 (73.2%) being females, with an average age of 74.4 years (Table 3), different from males who presented at a younger age of 66.2 years. Three studies mentioned patient factors like smoking, obesity, diabetes, and other cancers. Four of 21 (19.1%) patients were overweight/obese, and the same number were smokers. One study had a body mass index (BMI) average of 28.1 in a cohort of 11. Only one study mentioned previous primary malignancies in 10 of 50 (20%) cases. None of the cohort studies had data on the presentation symptoms of patients.

Carcinoembryonic antigen (CEA), Tumor size, and Location

Case series

Only 6 patients had CEA tested prior to surgery, with an average of 4.05 µg/L (normal 0–2.5 µg/L) and a range of 1.1–8.8 µg/L. Tumor size was 57.3 mm on an average

Table 1: General characteristics of MCC patients in our database.

TN stage	Age	Location	Extra-organ involvement imaging	PNI	LVI	Systemic therapy	Months since operation	Disease free
T2N0	56	ASC COLON	None	None	None	None	28	Yes
T2N0	75	CECUM	None	None	None	None	13	Yes
T3N0	75	CECUM	None	None	Yes	None	18	Yes
T3N0	70	ASC COLON	None	None	None	None	15	Yes
T3N0	86	ASC COLON	None	None	Yes	None	14	Yes
T3N0	85	DESC COLON	None	None	None	None	12	Yes
T3N1	93	CECUM	None	None	None	None	4	N/A
T3N1B	70	HEP FLEX	Abdominal lymph nodes	Yes	Yes	Pembrolizumab—refractory Capecitabine/oxaliplatin—complete response Bevacizumab—HTN	27	Yes
T3N1B	78	HEP FLEX		Yes	Yes	Capecitabine/oxaliplatin—enteritis (2 cycles)	24	Yes
T3N2	67	TV COLON		None	Yes	FOLFOX	14	Yes
T4BN1B	74	IC VALVE	Recurrence at anastomosis	None	Yes	Pembrolizumab—14 cycles	22	Ongoing

Abbreviations: ASC COLON: Ascending colon; DESC COLON: Descending colon; HEP FLEX: Hepatic flexure; HTN: Hypertension.

in maximal dimension, with a range of 40–95 mm, and 10 of 11 (90.9%) were within the right colon, with one (9.1%) in the transverse colon.

Case reports

Only 5 cases had CEA documented without exact levels, it was elevated in 20% of those patients. Tumor size was documented in 8 cases with an average of 67 mm, and 10 of 13 (76.9%) involved the right colon.

Cohort studies

455 of 1571 (29%) patients had raised CEA levels and one study had an average CEA of 2.8 µg/L in a sample of 11 patients. Tumor size was 70 mm with an average range of 63.8–96 mm in 6 studies, and 2700 of 3113 (86.7%) were discovered in the right colon.

Pathological staging and TNM staging

Case series

Eight of 11 (72.7%) patients had tumors T3 or higher, with 5 of 11 (45.5%) involving lymph nodes. There were no distant metastases; however, one patient had early recurrence at the anastomotic site, prompting a change in their systemic therapy regimen. Five (45.5%) patients had stage 3 disease or higher according to American Joint Committee on Cancer (AJCC) staging.

Case reports

Nine of 13 (69.2%) patients had T3 or higher tumors, with 7 of 13 (53.9%) patients with stage 3 or higher MCC. 5 of 13 (38.5%) patients had extra-organ metastases with spread to the liver or paraesophageal lymph nodes and pancreas (Table 2).

Cohort studies

Patients with stage 3 or higher disease were 447 of 1034 (43.2%), with 200 of 229 (87.3%) patients with T3 or higher disease (where study has explicitly mentioned T stage). Nearly 39% of patients had lymph node metastases (1087 of 2812) and 22 of 143 patients had extra organ metastases.

Treatment, follow-up, and survival

Case series

All patients proceeded to a right hemicolectomy, and 5 (45.5%) had node positive disease. Of these 5 patients, 4 were treated with systemic therapy, but 1 treated with surgery alone due to age. All patients are currently alive as of submission, and follow-up was an average of 17 months (range 4–28 months). One patient is still having ongoing systemic therapy of Pembrolizumab due to early recurrence (<6 months post-operatively) at the anastomotic site, with paraaortic lymph node involvement, and the highest grade of tumor T4bN1b—

Table 2: General characteristics of patients in the case reports

Article	Age	Sex	Presentation	Location	Size (mm)	Stage	Organ metastases	Follow-up (months)	Survival outcome
Romanzi et al. (2022) [10] Case 1	40	M	Abdominal pain, diarrhea	Rectosigmoid	ND	T4bN0M0	Negative	6	Alive
			Abdominal pain						
Martinotti et al. (2017) [11]	44	F	Abdominal pain	Right colon	60	T3N0M0	Negative	24	Alive
Kasapidis et al. (2015) [12]	58	M	Abdominal pain, NVD	Right colon	ND	T3N1bM0	Negative	38	Alive
Kelly (2022) [13]	63	F	IDA	Right colon	70	T3N0MX	Negative	ND	ND
Tatsuta et al. (2021) [14]	70	M	IDA	Right colon	ND	T4aN1bM0	Negative	10	Alive with palliative intent
Jain et al. (2014) [2]	72	F	PR bleeding	Left colon	80	T2N0M0	Negative	ND	Alive
Wakasugi et al. (2017) [15]	72	F	Paraneoplastic myopathy	Right colon	60	T3N0M0	Negative	12	Alive
Mitchell and Bendavid (2014) [16]	75	F	Abdominal pain	Right colon	40	T2 N2b M0	NOS	12	Alive

Table 2: *(Continued)*

Fatima et al. (2021) [4]	77	F	Weight loss, gait disturbance	Right colon	91	ND	Esophagus	ND	Died, Palliated
Cunningham et al. (2014) [17] Case 1	79	F	Malaise, nausea	Right colon	ND	T3N1M1	Esophagus and pancreas	5	Died
Romanzi et al. (2022) [10] Case 2	79	F	NVD	Transverse colon	ND	T4aN2bM1a	Liver	6	Alive with palliative intent
Cunningham et al. (2014) [17] Case 2	81	F	PR bleeding	Right colon	ND	T4N0M0	Negative	ND	Alive
Nguyen et al. (2014) [18]	81	F	Abdominal pain, nausea, fever	Right colon	70	T3N1bM0	NOS	7	Alive

Abbreviations: IDA: iron deficiency anemia; ND: not disclosed; Mets: metastasis; NVD: nausea, vomiting, diarrhea; PR: per-rectal.

this is no longer detectable on latest imaging. None of the case series patients have died.

Case reports

Four of 9 (44.4%) patients received systemic therapy post-operatively, 2 patients were treated palliatively due to age and comorbidities but were alive at time of writing the reports. Death was reported in 2 of 12 (16.7%) with one patient dying due to complications of systemic therapy and one due to post-operative complications. Follow-up had a mean of 13.3 (range 6–38) with an average range of 5–38 months in 10 cases.

Cohort studies

Of the 5 studies that mentioned systemic therapy, 151 of 155 (97.4%) patients had surgery and 65 of 155 (41.9%) patients had systemic therapy. Eleven studies mentioned survival in a multitude of ways with 53% survival in 7 studies, and 2 studies mentioning a 5-year overall survival of 42.9% and 72.7%. Two studies measured survival in months with one study differentiating poorly differentiated MCC with a 25.7 month mean survival months vs. 15.3 months in undifferentiated MCC, and another study defining survival at 80.1 months on average. Follow-up data in 8 studies averaged to 21.4 months ranging from 8–44 months (Table 3).

Tumor characteristics, BRAF and KRAS mutation

Case series

Eight of 11 patients had lymphovascular invasion and 2 of 11 demonstrated perineural invasion (Table 1). Immunohistochemistry (IHC) demonstrated loss of MLH1 and PMS2 expression in the tumors of all 11 patients with presence of MSH2 and MSH6. BRAF V600e mutations were absent on staining in 2 of 11 (18.8%) of patients and stains CK7, CK20, and CDX2 were positive in 20%, 18.2%, and 63.6% respectively.

Case reports

There was sparse data on tumor characteristics with 1 of 3 samples having PNI, and LVI 2 of 3 (Table 3). Similarly, for KRAS and BRAF mutations, only 5 patients were tested for either. Two of 4 patients were BRAF positive, and 1 of 3 patients was KRAS wild type. MLH1 was negative in the tumors of 10 of 11 patients (90.1%).

Cohort studies

Out of 1897 patients, 302 (15.9%) had PNI with 1133 of 2151 (52.7%) demonstrating LVI. MLH1 testing was available for 192 patients, with 93.8% having loss of MLH1. Stains CK7, CK20, and CDX2 were 7.4%, 26.4%, and 45.7% positive, respectively. Four studies mentioned KRAS mutation with 238 of 313 (76%) (Table 4).

DISCUSSION

Given MCC's reported incidence of 0.03% [10] of all colorectal cancers and its unique clinicopathological, immunohistochemical, and prognostic profile, there is limited data currently available about this rare subtype. This study demonstrates some interesting findings regarding MCC.

The mean and median age in our case series was 75 years, compared to the average of 70 years in the pooled cohort studies. The occurrence of MCC among female patients was also higher at a ratio of 3:1, compared to 2:1 in the literature [28], which included one study with an overrepresentation of males at 70% [3].

Six of 11 patients presented with iron deficiency anemia or a positive fecal occult blood test investigated by

Table 3: Demographics, staging, and survival of cohort studies

Article	Sample	Female	Male	Age	Female age	Male age	Stage 1	Stage 2	Stage 3	Stage 4	T1/T2	T3	T4	Local mets	Liver mets	Mets NOS	Surgery	Systemic therapy	Follow-up in months	Progression	Recurrence	Death	5 year OS%	Survival
Abada et al. (2023) [19]	11	7	4	69				8	1	2														
Arai et al. (2004) [20]	23	16	7	80.6													23						2 out of 10 died	
Fiehn et al. (2015) [21]	9	4	5	76								7	2											
Friedman et al. (2016) [22]	105	86	19	78.9			9	51	41	2														
Gómez-Álvarez et al. (2017) [3]	10	3	7	57							2	5	3				10	10	6	32	3	2	3	42.90%
Gupta et al. (2020) [23]	33	26	7	79			2	12	16	1						7	33	31	6	31.6				25.7 months PD MC and 15.3 months UD MC
Hinoi et al. (2001) [24]	15	9	6	64.3													15			64.8			7 out of 14	
Jabbal et al. (2022) [7]	2709	1963	746	74	75	70	195	276	195	152							2709							80.1 months survival
Jessurun et al. (1999) [1]†	11	11	0	53.7				2	7	1					2		11			21.6 of 8 patients			2 out of 8	
Lasota et al. (2020) [25]	2	2		76.5	76.5						1	1												
Lin et al. (2014) [26]	18	13	5	79	78	83.2						78		1	1									
Rüschoff et al. (1997) [27]	20	11	9	59.85	70.3	47.1					3	9	8			4	20	20		31		1	6	
Scott et al. (2021) [8]	33	25	8	79							2	18	13											
Thirunavukarasu et al. (2010) [28]	50	34	16	69.3	72.1	64.3	6	22	17	5	10	24	16			5	50	50		24				11 pts died out of 43 follow-up
Wick et al. (2005) [29]	68	68	0	71						44 stage 3 or 4							68	68	44	60			27 in 5 years	
Winn et al. (2009) [30]	16	14	2								10	5	1				16	16		38.9				15% died of disease number followed up
Zenger et al. (2020) [31]	11	10	1	61			1	3	5	2	1		10			2	11	11						72.70%
Total/Mean	3144	2302	842	70.5	74.38	66.15	213	374	282	165	29	147	53	1	3	18	2966	206	18.66		3	3	34	

† Clinical data for 1 patient not available.

UD: Undifferentiated, PD: Poorly Differentiated, MC: Medullary colon cancer.

Table 4: Immunohistochemistry staining and BRAF results in cohort studies, case series, and case reports

	Cohort studies		Case series		Case reports	
	Total tested	Positive	Total tested	Positive	Total tested	Positive
MLH1	96	6.25%	11	0%	11	9.09%
PMS2	25	4%	11	0%	10	10%
MSH2	27	40.74%	11	100%	8	87.50%
MSH6	12	91.67%	11	100%	7	85.71%
BRAF	9	33.33%	11	81.82%	4	25%
CK7	54	7.40%	10	20%	7	28.57%
CK20	53	26.42%	11	18.18%	5	0%
CDX2	70	45.71%	11	63.64%	6	50%
Synaptophysin	131	19.08%	9	0%	3	0%
Chromogrannin A	115	20.87%	9	0%	3	0%
Calretinin	54	50%	2	0%	4	100%

the Australian National Blood Supply Contingency Plan (NBSCP) or their general practitioner (GP), reinforcing the importance of age-based screening with reduction of mortality by 23% [32].

American Joint Committee on Cancer Stage 3 disease was higher in our group with 45.5% vs. 38.7% in the literature. Contrary to much of the literature, one study demonstrated a poorer prognosis in MCC patients with stage 3 disease vs. other non-MCC cancers with a survival of 15.3 months vs. 47.2 months p=0.001 [13]. Location of the tumor was in the right colon with 100% of our patients undergoing a right hemicolectomy. Right colonic involvement was similar in the literature review with 86.7% involvement of the colon. Tumor size was smaller in our cohort at 57 mm, with 70 mm average in the cohort studies, and generally MCC is known to present with larger sizes in comparison to other poorly differentiated or undifferentiated adenocarcinomas [7].

Survival in our case series was 100% vs. 16.6% mortality in the pooled case reports and 53% in the observational cohort studies. This is likely biased by our short follow-up time of 17 months average (range 4–28 months). One patient had an early recurrence of disease at the anastomotic site despite having a clear margin resection, with TNM score of T4bN1bM0.

Pathologically, MCCs can be differentiated from other undifferentiated carcinomas by strong calretinin staining and loss of MLH1 and CDX2 staining [10], often CDX2 is positive in colorectal adenocarcinoma [33]. Our case series identified 2 specimens where calretinin was negative, with lack of expression of CK20, CK7, and chromogranin A with weak or focal CDX2 staining. However, in these cases, SATB2, which has been demonstrated to be positive in 95% of colorectal cancers [34], demonstrated positive staining while MLH1 and PMS2 were absent. Morphologically both tumors favored a diagnosis of MCC.

There are limitations with this study. Firstly, with regard to our case series, the cohort was too small a number to make any definitive conclusions about MCC. Due to the small population size, the follow-up period had a large range, and none of the patients reached 5-year survival mark at the time of writing the study. Patient demographic data on BMI and smoking history were surprisingly sparse. Pathological staining was variable; however, our institution routinely investigated MMR proteins and BRAF.

Pertaining to the literature review, the search could have been improved by performing our search on a third database, and given MCC relatively new classification, there may be other terms outside of uncommon search terms such as solid-type poorly differentiated adenocarcinoma—this term however was included.

CONCLUSION

Medullary carcinomas tend to affect females more than males, and generally occur in the right side of the colon. Given the rarity of this sub-type, surgeons and pathologists are encouraged to continue contributing longitudinal data to inform future management pathways.

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