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Case Report

Metastatic Merkel Cell Carcinoma In The Splenic Flexure Of The Colon Mimicking Primary Colonic Carcinoma-A Case Report With Literature Review

Pramath Kakodkar[1], Dana Diudea[1], Selliah C. Kanthan[2], and Rani Kanthan[1*],

[1]Department of Pathology and Laboratory Medicine, Royal University Hospital, 103 Hospital Dr, Saskatoon, SK S7N 0W8, Canada.

[2]Division of General Surgery, College of Medicine, University of Saskatchewan, Saskatoon, Canada.

[*]**Corresponding author:** Rani Kanthan, Department of Pathology and Lab Medicine, Royal University Hospital, 103 Hospital Dr, Saskatoon, SK S7N 0W8, Canada.

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Abstract

Background: Merkel Cell Carcinoma (MCC) is an unusual neuroendocrine neoplasm that usually presents as a primary malignant skin tumor with localized disease. Distant metastasis is uncommon with metastases to the colon being extremely rare. In this case report, we discuss MCC metastasis to the colonic splenic flexure that mimicked primary colon carcinoma. A literature review is also undertaken. **Case presentation:** An 82-year-old man presented with melena and microcytic anemia accompanied by moderate weight loss. Upon investigation, a computer tomography of the abdomen showed a 5 x 3 cm apple core-type lesion at the splenic flexure. Colonoscopy revealed a circumferential ulcerated large mass in the splenic flexure which was biopsied for pathological conformation of presumed colonic carcinoma. Detailed histopathological evaluation of the endoscopic mucosal biopsies with additional immunostaining confirmed the diagnosis of metastatic MCC. Review of his medical records confirmed MCC in the right axillary lymph nodal dissection 3 years ago from an unknown cutaneous primary. Due to accompanying medical comorbidities palliative supportive management was opted. He died a month later from pneumonia and decompensated cardiac failure. **Conclusion:** MCC metastasis to the colon is an extremely uncommon event. Clinically and radiologically it often mimics a primary colonic carcinoma. Histopathological diagnosis from endoscopic mucosal biopsies by light microscopy alone remains a challenge. Additional immunohistochemical stains are essential for accurate diagnosis. The presence of colonic metastases probably indicates widespread disease as most cases like ours are associated with an extremely high mortality rate. Earlier diagnosis with interventional multimodality treatment options may alleviate this dismal prognosis.

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Keywords: Merkel Cell Carcinoma; Endoscopic Biopsy; Uncommon Mucosal Metastasis

Introduction

Merkel Cell Carcinoma (MCC) is designated as a high-grade primary cutaneous neuroendocrine carcinoma in the current iteration of the World Health Organization (WHO) classification of Endocrine and Neuroendocrine Tumors [1]. This rare entity was first described by Toker in 1972 as a trabecular carcinoma of the skin [2]. Though, the precise cell of origin of MCC remains contentious in the literature, Merkel cells are favored as the cellular progenitor of MCC as they bear histologic and phenotypic similarities as being the only neuroendocrine cells native to the epidermal stratum basale [3].

MCC has a predilection for occurring in the elderly or immunosuppressed, male patients, and classically presents as a painless, rapidly growing violaceous cutaneous lesion arising on the sun-exposed sites of the head and neck [4, 5]. MCC predominantly presents as a localized cutaneous disease (65%) or with regional lymph node metastases (26%), and in a minority of patients with distant metastases (8%) [4]. The Surveillance, Epidemiology, and End Results (SEER) database showed that the 10-year survival rate for MCC was 71%, 48%, and 20% for localized cutaneous disease, regional lymph node metastases, and distant metastases, respectively [6]. The commonest sites for MCC metastasis include distant lymph nodes (60.1%), distant skin (30.3%), lung (23.4%), brain (18.4%), and bone (15.2%) [7]. Metastatic MCC involving the GI tract is an uncommon event with limited evidence based publications [8].

We present a case of metastatic MCC to the colon that on clinical, radiological, and at colonoscopy was presumed to represent primary colonic carcinoma. The endoscopic biopsy however revealed the presence of an uncommon lesion which with additional immunohistochemistry was accurately recognized as metastatic MCC. A previous history of MCC from a presumed unknown cutaneous primary (MCCUP) was confirmed in a right axillary node dissection three years ago. A comprehensive literature review is also performed to summarize the clinical and pathological insights into cases with metastatic MCC to the colon. The primary objective of our case report is to increase awareness of such uncommon metastases being diagnosed from endoscopic biopsies for a presumed primary colonic carcinoma. Accurate recognition of these uncommon lesions is vital for the discussion of relevant management options that need to be tailored on an individual basis.

Case Presentation

An 82-year-old gentleman presented to the emergency department with increasing confusion and melena over 5 days. This gentleman had complex comorbidities notable for Heyde syndrome, heart failure with reduced ejection fraction (EF= 39%), multivessel coronary artery disease, severe aortic stenosis, well-controlled type 2 diabetes mellitus, and atrial fibrillation managed on apixaban. He endorsed a 20-pounds unintentional weight loss over the past year. Physical examination was otherwise unremarkable. Laboratory tests revealed microcytic anemia and prerenal acute kidney injury, and other biochemical tests were all within normal ranges.

In the emergency department, to correct his hypovolemic and microcytic anemia, resuscitation with crystalloid fluid and blood transfusion with 4 units of packed red blood cell were given. Initial colonoscopy was terminated due to multiple unsuccessful attempts to reach the transverse colon related to significant left-sided diverticulosis and inadequate bowel prep. Computer Tomography (CT) enterography (Figure 1) was performed which showed an apple core-type lesion (5 x 3 cm) at the splenic flexure devoid of active bleeding. Repeat colonoscopy evaluation further characterized this lesion as a circumferential ulcerated large mass at 65 cm with an appearance highly suspicious for colonic cancer. Endoscopic mucosal biopsies were procured for pathological analysis, and the patient was transferred to medical oncology with the preliminary diagnosis of primary colon cancer.

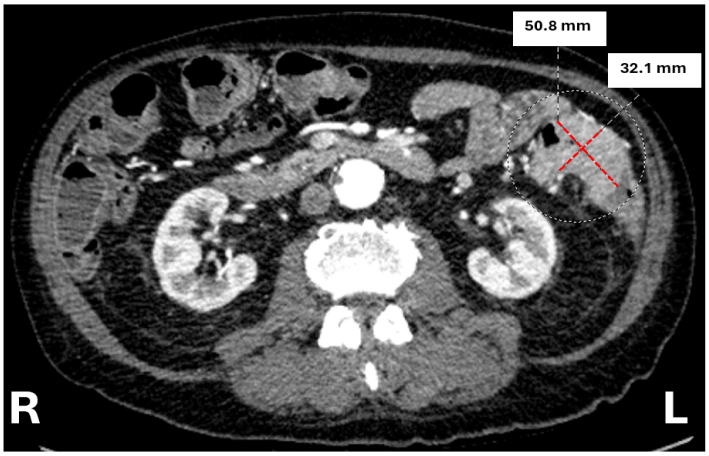


Figure 1: Abdominal CT with triple phase enterography

Histopathological evaluation of the left-sided colon mucosal biopsy revealed fragments of ulcer and colonic mucosa with expansion of the lamina propria with sheets of malignant cells (Figure 2A). The basaloid neoplastic cells show a solid architecture, composed of small cells with elongated nuclei, scant cytoplasm, and increased mitotic figures (Figure 2B). Immunohistochemical (IHC) staining of these neoplastic cells showed them to be strongly positive for pan cytokeratin, (Figure 2C), synaptophysin and

chromogranin (Figure 2D). There was no expression of CK7 while Cytokeratin 20 (CK20) showed the classic dot like positivity of the neoplastic cells in contrast to the strong membrane staining of the adjacent colonic glands as seen in Figure 2E. The noncolonic origin of the neoplastic cells was also supported by no expression of CDX2 with strong internal control staining of the colonic glands as seen in Figure 2F. Additional IHC stains expressed in the neoplastic cells were CD117 and Ber-EP4. There was no expression of CD3, CD 20, CDX2, TTF1, NKX3.1, GATA3 and PAX8 immunostains in the neoplastic cells. The Ki-67 proliferating index was over 90%. The histological appearance and the pattern of IHC staining was consistent with Merkel cell carcinoma. Retrospective medical chart review yielded a pathology report from 3 years ago which showed that the patient had a right axillary lymph node dissection that reported MCC metastatic to the lymph nodes from an Unknown Cutaneous Primary [MCCUP]. He had refused adjuvant radiotherapy at that time. This confirmed the diagnosis of an uncommon mucosal metastatic lesion of Merkel cell carcinoma in these colonic biopsies in contrast to the expected primary colonic carcinoma.

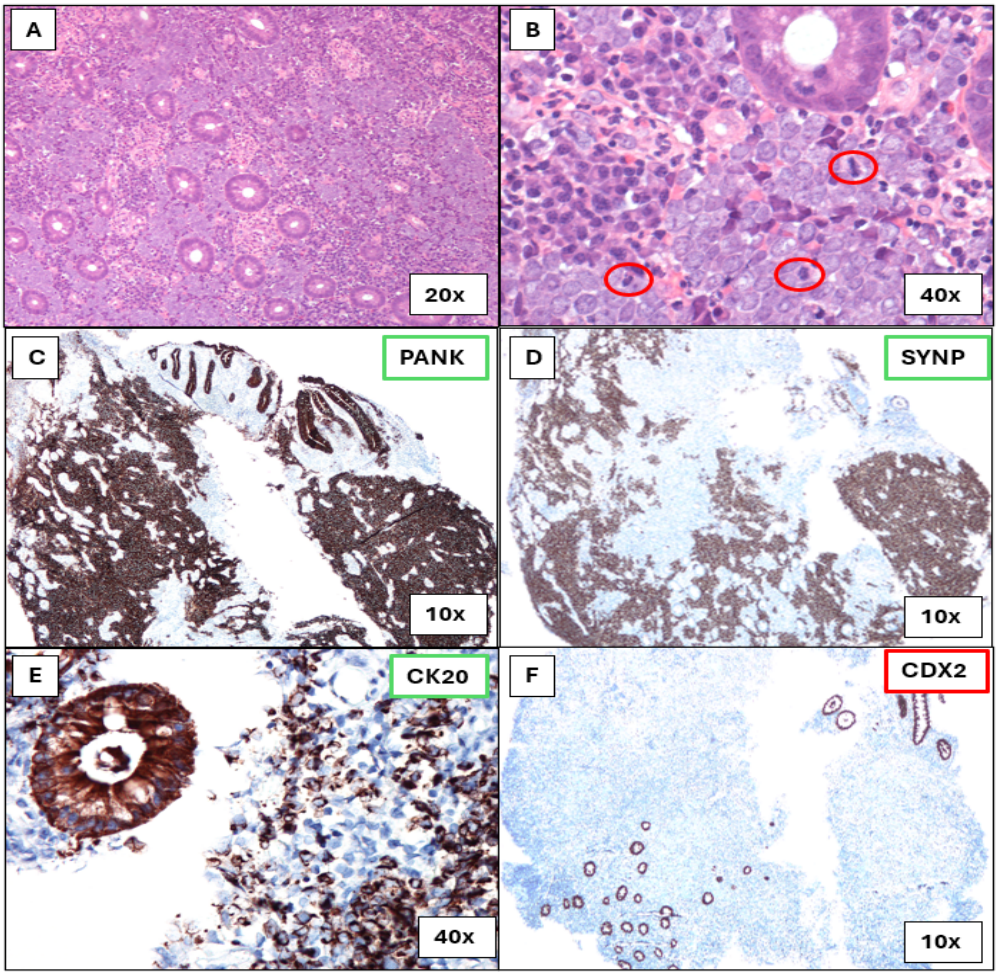


Figure 2: Summary of key histopathological findings seen in the endoscopic mucosal biopsy

Laparoscopic resection and palliative chemotherapy were offered to the patient; however, due to his complex cardiac history and high cerebrovascular accident risk, non-operative supportive management was opted for. Our patient unfortunately passed away 25 days after the colonoscopy from acquired pneumonia and decompensated cardiac failure.

Discussion

Merkel Cell Carcinoma (MCC) is an aggressive, primary cutaneous endocrine neoplasm that predominantly presents as a localized cutaneous disease (65%) [4]. Up to 26% of MCC have regional lymph node metastases at presentation [4]. Distant metastases are rarely observed (8%) with common sites being lymph nodes (60.1%), distant skin (30.3%), lung (23.4%), brain (18.4%), and bone (15.2%) [7]. The literature review showed that colorectal metastasis from MCC is rare. Furthermore, such metastases from MCCUP like our case is exceedingly rare in the published English literature [9, 10]. This case report will be the third case of MCCUP metastasizing to the colon as seen in Table 1.

Site of MCC metastases	Age (sex)	Primary MCC site, Tx (duration to colon metastasis)	Presentation	Radiology	Endoscopy findings	Treatment	Outcome (Follow-up duration)	Ref.
Cecum and ileocecal valve	74 (F)	Skin right forearm and axillary LN. WLE, LA, and adjuvant RTx. (1.5y)	Palpable mass RUQ, bowel obstruction symptoms	CT: Tumor in the ileocecal valve extends into cecal lumen with mesenteric lymphadenopathy	Tumor at 70 cm from the anus	Palliative intent surgery (lap right hemi-colectomy)	Death (28 months)	[11]
Cecum and ascending colon	86 (M)	Left leg. WLE. (2y)	Bowel obstruction symptoms	PET: suspicious avidity within the cecum and liver. CT: 5 cm obstructing tumour in the caecum	NA	Palliative intent surgery (lap right hemi-colectomy)	Death (14 weeks)	[12]
*** **Ascending colon (proximal)**	71 (M)	Unknown, Metastasis to Right axillary LN. WLE, LA, and adjuvant RTx. (3y)	Hematochezia	PET: new intense uptake soft tissue nodule in colon at 2 years follow up.	Partially obstructing tumor in proximal ascending colon.	Pembrolizumab (22 cycles)	Stable	[10]
*** **Ascending colon (hepatic flexure)**	69 (F)	Unknown	Progressive abdominal pain, distention, and constipation	CT: large bowel obstruction with right colon mass	Stricture, edema, and necrotic mass at hepatic flexure	Palliative (Right hemicolectomy), hospice care without CTx	Death	[9]
Ascending colon (polyp)	70 (F)	Left inguinal LN. LA, adjuvant RTx and Carboplatin. (5y)	Progressive lower back pain, and weakness over 1 month	CT: bulky retroperitoneal adenopathy	Semi-sessile polyp smooth, pale, un-remarkable margins, and mucosa.	Cisplatin and etoposide (4 cycles), Cyclo-phosphamide, doxorubicin, and vincristine (8 cycles)	Stable	[13]

Transverse colon	71 (F)	Skin, jejunum metastasis. Skin WLE, neoadjuvant CTx [etoposide and carboplatin], partial enterectomy. (4y)	Hematochezia and diarrhea	NA	Partial obstructing, edema, and friable circumferential mass	Palliative (Hospice care without CTx)	Death (6 months)	[14]
Transverse colon	74 (M)	Skin with metastasis to parotid. Superficial parotidectomy, LA, and adjuvant RTx. (2y)	Bowel obstruction symptoms	NA	large obstructive mass	Colon resection surgery, adjuvant RTx and high dose CTx (4 cycles of etoposide and carboplatin every 3 weeks)	Stable (6 years)	[15]
Descending colon	60 (M)	Left arm, axillary LN and mediastinal metastases. WLE, LA, and CRTx. (4y)	Constipation and obstipation	CT: Carcinomatosis with perforated viscus and abscess	NA	Palliative intent resection (Extended Left hemicolectomy), hospice care without CTx	Death	[16]
Descending colon	62 (M)	Neck. WLE. (6y)	Progressive right axillary and left inguinal lymph-adenopathy and unintentional weight loss over 5 months.	CT: Soft tissue lesion in the descending colon	Ulcerating mass at 45 cm from the anus	Carboplatin and etoposide	Death (4 weeks)	[17]
*** **Descending colon**	82 (M)	Unknown, Metastasis to Right axillary LN. LA. (3y)	Increasing confusion and melena over 5 days	CT: Apple core-type lesion at the splenic flexure	Circumferential ulcerated large mass at 65 cm	Hospice care without CTx	Death (4 weeks)	**This case**

Abbreviation: Computer Tomography (CT); Chemotherapy (CTx); Chemoradiotherapy (CrTx); Female(F); Lymph Node (LN); Lymphadenectomy (LA); Male (M); Not Available (NA); Positron Emission Tomography (PET); Radiotherapy (RTx); Right Upper Quadrant (RUQ); Reference (Ref.); Treatment (Tx); Wide Local Excision (WLE); MCCUP- Merkel Cell Carcinoma Of Unknown Primary

Table 1: Literature review summarizing the clinical and pathological parameters of MCC metastatic to the colon.

Our literature review, limited to the English language, yielded 9 cases with documented metastatic MCC to the colon (Table 1). The patients in our literature review cohort had an average age of 71.9 ± 7.5 years with a 1.5 fold male predilection (M:F = 6:4). The predominant presenting complaints in these patients were symptoms associated with bowel obstruction or per rectum bleeding. CT imaging results did not show any laterality. MCC metastasis to the colon was uniformly distributed across from the cecum to the descending colon. The prominent endoscopic findings for MCC were stricture formation, edema, and/or ulceration subjacent to a circumferential mass. The predominant goal of management was palliative intent in these patients. Even with this smaller sample size (n=10) it can be gleaned that the mortality rate for MCC metastasizing to the colon remains abysmally high at 70% by 7.9 ± 10 months. With a larger dataset the extrapolated overall survival at 10 years for this cohort might even approach less than 10%. This highlights the aggressive nature of MCC metastasizing to the colon.

The histopathological diagnosis of MCC can be particularly challenging as they are often not considered in the differential diagnosis when they occur in rare distant metastatic sites such as the colon. In a recent review of 55,154 consecutive endoscopic colorectal biopsies from our laboratory only 52 (0.4%) were identified as cases representing the presence of non-colonic mucosal metastases [8]. A biopsy diagnosis of primary MCC by light microscopy alone is extremely challenging due to the overlapping histopathologic features between MCC and other poorly differentiated small round blue cell tumors such as small cell carcinoma, lymphoma, neuroblastoma, Ewing's sarcoma, and melanoma [18]. The cytology of MCC is described as round to oval nuclei, hyperchromatic nuclei with finely stippled (salt-and-pepper) chromatin, inconspicuous nucleoli, with scant cytoplasm and neuroendocrine granules [18]. These neoplastic cells are arranged in trabeculae, sheets, or cords and show high mitotic rate, vascular invasion, as well as interspersed lymphoplasmacytic infiltrates. Therefore, though MCC's neuroendocrine features maybe suspected from its characteristic cytology, the overall histological appearance is not distinct enough to rule out other small blue round cell tumors entities such as poorly differentiated adenocarcinomas, and small cell variant of malignant melanoma [18]. Definitive diagnosis relies on the immunohistochemical profiling of the neoplastic cells. MCC expresses neuroendocrine markers such as synaptophysin (92%), chromogranin-A (84%), neuron specific enolase (80%), and CD56 (88%). Cytokeratin 20 (CK20) is the most specific marker and shows the characteristic perinuclear punctate or dot-like positivity [19]. The IHC specificity (94%) and sensitivity (88%) for MCPyV's large T-antigen shows potential for optimized detection of the MCPyV subset of MCC [20]. In this case report, our patient's metastatic MCC showed positivity for BerEP4. BerEP4 positivity is a common feature of all Neuroendocrine Carcinomas (NEC), basaloid epithelial tumor of the skin, and does not aid in distinguishing MCC from other NEC. Interestingly, though BerEP4 could be utilized as a surrogate marker for the detection of MCPyV; as higher BerEP4 expression levels are seen in MCPyV-positive cases 57% (n= 46 out of 81) compared to MCPyV-negative cases ($p<0.0003$) [21]. MCPyV detection would also facilitate consideration of immune checkpoint inhibitor therapy. Supplementary table S1 summarizes the IHC panels performed, and results reported as available for each patient in our Literature review.

Site of MCC metastases	Age (sex)	Comorbidities	Lab findings	Histology	Positive IHC	Negative IHC	Ref #.
Cecum and ileocecal valve	74 (F)	NA	NA	Mucosa infiltration, Basaloid neuroendocrine cells. High proliferation. Vascular invasion and multiple LN involvement	CK20, ChgA, CD56, MNF116.	CD3, CD30. CD10, CD20, CD23, CD5	[11]
Cecum and ascending colon	86 (M)	Afib, MI, HTN, CHF. Multiple excised non-melanoma skin lesions.	Anemia (Hgb 108g/L)	Submucosal and muscularis propria Infiltration	NA	NA	[12]

*** **Ascending colon (proximal)**	71 (M)	HTN, Afib, CVA, CAD, COPD	Anemia (Hgb 97mg/L)	Invasive basaloid neuroendocrine cells.	CK20, CD56, SYNP, CgA. KI-67=55%	CK7, S100, SOX10	[10]
*** **Ascending colon (hepatic flexure)**	69 (F)	bilateral IDC, Pulmonary adenocarcinoma, and anal SCC. History of radiation exposure to the colon.	NA	Invasive basaloid neuroendocrine cells. High proliferation. Extending into the pericolic adipose tissue to the radial margin, with serosal and subserosal deposits	AE1/ AE3, SYNP, MCPyV Ki-67=98%	NA	[9]
Ascending colon (polyp)	70 (F)	Multiple basal and squamous cell cancers.	Microcytic anemia (Hgb 71 g/L)	Mucosa and submucosa infiltration.	CK20, SYNP, ChgA	CK7 and TTF1	[13]
Transverse colon	71 (F)	Stress cardiomyopathy, asthma, MI	Anemia (Hgb 108 g/L)	Invasive basaloid neuroendocrine cells.	CK20, PANK, SYNP, ChgA, CD56	CK7 and TTF1	[14]
Transverse colon	74 (M)	Ex smoker for 30 pack years	NA	Invaded beyond the serosa, involve the abdominal wall with close excision margins. Metastasized to three LN	Positive: CK20	NA	[15]
Descending colon	60 (M)	History radiation and immune suppression	Anemia (Hgb 104g/L)	Extending into the peri-colonic and abdominal wall soft tissue.	CK20, PANK, SYNP	NA	[16]
Descending colon	62 (M)	MI, HTN, T2DM, hyperlipidemia, EtOH misuse	Macrocytic anemia, FOB positive	Invasive basaloid neuroendocrine cells.	CK20	NA	[17]
*** **Descending colon**	82 (M)	Heyde syndrome, HFrEF, CAD, severe AS, T2DM, and Afib	Microcytic anemia (hgb 71g/L)	Solid architecture, high mitotic proliferation	CK20, PANK, SYNP, ChgA, CD117, Ber-EP4.	CD3, CD20, CDX2, TTF1, NKX3.1, GATA3, PAX8	This case

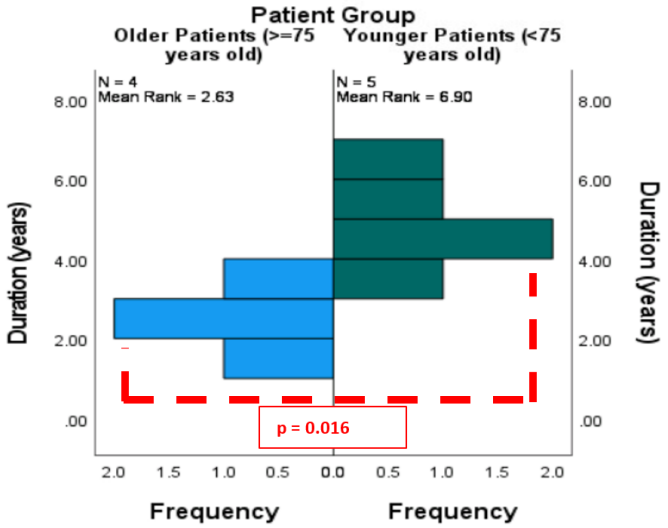
Abbreviations: Atrial Fibrillation (Afib), Aortic Stenosis (AS), Coronary Artery Disease (CAD), Congestive Heart Failure (CHF), Chromogranin-A (Cga), Chronic Obstructive Pulmonary Disease (COPD), Cerebral Vascular Accident (CVA), Cytokeratin (CK), Ethanol (Etoh), Fecal Occult Blood (FOB), Female (F), Hypertension (HTN), Heart Failure Reduced Ejection Fraction (Hfref), Hemoglobin (Hgb), Invasive Ductal Carcinoma (IDC), Immunohistochemistry (IHC), Lymph Node (LN), Male (M), Myocardial Infarction (MI), Not Available (NA), Neuron Specific Enolase (NSE), Pancytokeratin (PANK), Squamous Cell Carcinoma (SCC), Synaptophysin (SYNP), Type 2 Diabetes Mellitus (T2DM)
***MCCUP- Merkel Cell Carcinoma Of Unknown Primary

Supplementary Table S1: Literature review – This table summarizes the comorbidities, laboratory findings and the key histopathological findings reported with their Immunohistochemical profile.

The patients in our literature review formed a bimodal distribution: older patients (>= 74 years, n=4, average age of 79.0 ± 5.2 years old) and younger patients (<74 years, n=5, average age of 66.8 ± 4.8 years old). The duration of time from primary MCC to recurrent distant metastases was shorter (independent Mann-Whitney U test, p=0.016) in the older patient cohort (2.1 ± 0.5 years) compared to the younger patient cohort (4.4 ± 1.0 years) as shown in supplementary table S2 and supplementary Figure S1. The shorter duration from primary MCC to distant metastasis observed in the older patient cohort could be explained by aging associated immunosenescence. The mitigated antiviral immune response in older age can potentially propagate MCPyV mediated carcinogenesis. Merkel Cell Polyomavirus (MCPyV) infection (80% of MCC cases) and Ultraviolet (UV) induced mutagenesis reflect the two divergent pathways that propagate carcinogenic transformation of the progenitor cell to MCC [20, 22]. The MCPyV negative subtype is considered a negative clinical prognostic indicator due to its aggressive clinical course. This may be related to higher genomic instability and somatic mutational burden in drivers such as TP53, RB1, HRAS, KRAS, and NOTCH as observed in MCPyV negative subtype [20]. In the literature, majority of the cases of dermal MCC (60-80%) are of the MCPyV positive subset in [20, 23]. Despite this reported prevalence, only one out of the 10 cases in table 1 had been tested for MCPyV status [9].The prognosis overall in MCC is mainly dependent on tumor size, nodal involvement, presence of distant metastasis, and MCPyV status. The SEER database showed that the 10-year mortality rate for MCC was 80% with distant metastasis [6].

Total (N)	9
Mann-Whitney U	0.500
Wilcoxon W	10.500
Test Statistic	0.500
Standard Error	4.031
Standardized Test Statistic	-2.357
Asymptotic Sig. (2-sided test)	0.018
Exact Sig. (2-sided test)	0.016

Supplementary Table S2: Comparison of Duration from primary MCC to metastatic MCC in the literature review patients groups: elderly (>=74 years), and young (<74 years).



Supplementary Figure S1: Comparison of Median duration from primary MCC to metastatic MCC in the literature review patient groups: older (blue), and younger (green).

The current management strategy for symptomatic primary MCC is aggressive locoregional treatment via surgery and adjuvant radiotherapy [24]. Conversely, locally advanced and metastatic MCC are often managed with a single-agent anti-PD1/PD-L1 checkpoint inhibitors (nivolumab, pembrolizumab, and avelumab) or conventional chemotherapy (platinum agents, cyclophosphamide, doxorubicin, vincristine and paclitaxel) [25].

Our literature review shows only 3 out of 9 cases of MCC with colon metastasis attained clinical remission [10, 13, 15]. Compared to our patient, all three case reports utilized adjuvant radiotherapy at the first occurrence of MCC. Adjuvant radiotherapy was refused by our patient when MCC was first detected in his right axillary lymph nodes. Contrastingly, Shobha et al. utilized immunologic only treatment with Pembrolizumab which facilitated the MCC stromal microenvironment immune cells and cytotoxic T-cells to detect and eliminate MCPyV integrated MCC cells. In addition, Shobha et al. also used Positron Emitting Tomography (PET) scan monitoring their patient at 2-year follow up from their first detection of MCC which identified ascending colon increase avidity a year prior to the clinical presentation of hematochezia [10]. Conversely, Tuktamyshov et al. utilized high

dose chemotherapy and Veness et al. utilized surgical resection with high-dose adjuvant radiochemotherapy [13, 15]. Based on our limited sample size in our literature review it can be inferred that distant metastases of MCC if treated early with immune checkpoint inhibitor as first-line immunological therapy agents may lead to clinical remission. In this context, we also suggest utilizing annual PET scans as part of the follow-up protocol in elderly patients diagnosed with MCC for early detection of distant metastases.

Since the mortality rate of patients with MCC metastasizing to the colon is so high, novel avenues for diagnostic and monitoring of MCC needs to be explored. The Circulating Tumor Cell (CTC) assay in MCC shows potential as it is evolving into a valuable ancillary test. In 15 patients with regional nodal MCC, blood samples yielding a CTC-negative or CTC positive result led to 80% and 29% progression free survival at 2 years in these patients, respectively [26]. This CTC test may have been beneficial in providing our patient in the case report with prognostic information to persuade adjuvant radiotherapy at his first occurrence of right axillary nodal metastasis. Future studies in this area can yield an optimized integration of the CTC assay into the follow-up protocol guidelines of MCC with known nodal metastasis.

Conclusion

Merkel cell carcinoma is an aggressive primary cutaneous neuroendocrine neoplasm that can rarely metastasize to the colon. Distant metastasis of MCC is associated with an exorbitant mortality rate and therefore MCC should always be considered in the differential in cases of uncommon lesions seen in endoscopic mucosal biopsies especially in patients with a known history of MCC. Detailed immunohistochemical profiling of the neoplastic cells is vital for accurate pathological diagnosis. We recommend consideration of the utilization of PET scan-based follow-up in patients with primary or locally metastasized MCC as well as implementation of checkpoint inhibitors as alternative options for first-line treatment for MCC with distant metastasis.

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Ethical Consideration: None

Conflict of Interest: The authors declare no conflicts of interest.

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