

Isolated Cerebellar Metastasis as the Initial Manifestation of Right-Sided Colon Cancer: A Case Report and Review of Current Management Strategies

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Introduction

A 55 year old female with no significant past medical history presented to her local physician with a 2-week history of right hand incoordination and progressive gait instability. She had no family history of malignancy, and denied weight loss, appetite change, nausea, fatigue, abdominal pain, weakness, fevers, chills, or night sweats.

An MRI of her brain revealed an extra-axial-appearing cerebellar tumor (**Figure 1**) that exhibited characteristics of a meningioma. A complete blood count revealed a mild normocytic anemia with hemoglobin of 11.0 mg/dl, and a chemistry panel with ionized calcium was normal. Pre-operative steroids were administered, and the mass was resected with satisfactory post-operative course and resolution of neurologic symptoms. Pathology revealed a metastatic poorly-differentiated carcinoma. Immunohistochemical stains were positive for AE1/AE3, CDX2, CK7, CK20, and CAM5, consistent with a non-neuronal, gastrointestinal origin.

A subsequent CT of her chest, abdomen, and pelvis revealed a 4.6 × 4.2 × 2.7 cm centrally necrotic mass along the medial aspect of the cecum and ascending colon, concerning for a primary colon malignancy. Interestingly, no liver, lung, or bone metastases were observed (**Figure 2**). An ensuing colonoscopy revealed a lesion in the ascending colon and a biopsy confirmed an intermediate-grade adenocarcinoma. She had never undergone screening colonoscopy prior to her diagnosis.

Post-craniotomy, she underwent whole-brain radiation therapy, followed by right-sided hemi-colectomy. Pathologic evaluation revealed invasion into peri-colonic adipose tissue with 7/22 mesenteric lymph nodes positive for adenocarcinoma, consistent with pT3N2bM1 stage IV disease. She underwent 12 cycles of adjuvant modified FOLFOX6 chemotherapy without complications.

Thirteen months later, multiple 1.5 cm hepatic lesions were discovered on a surveillance CT abdomen. Biopsy and mutation analysis revealed KRAS wild type metastatic colorectal cancer. She was re-initiated on FOLFOX6+bevacizumab therapy, but developed a significant reaction during the second oxaliplatin infusion, prompting a switch to FOLFIRI+bevacizumab. Progression

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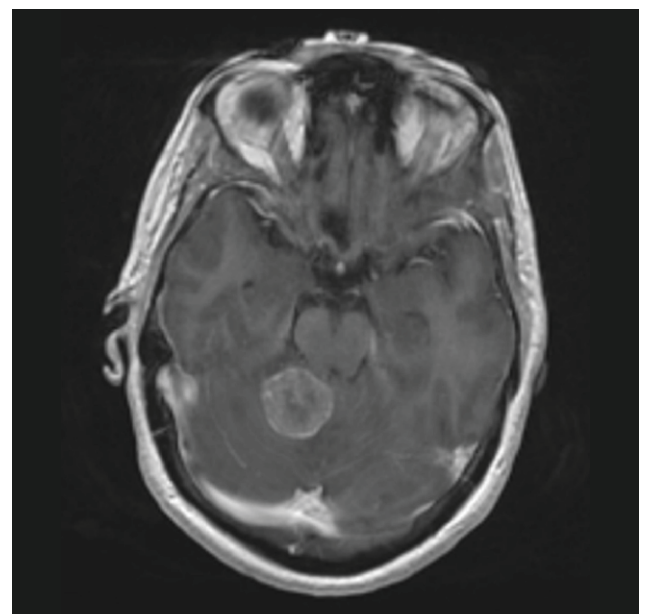


Figure 1 Brain MRI depicting the 2.5 cm well circumscribed, homogeneously enhancing mass along the inferior surface of the right tentorial leaf.

of liver metastases after 2 cycles of this regimen was observed, prompting replacement of bevacizumab with cetuximab, and continuation of FOLFIRI. After 7 months of disease response with FOLFIRI+cetuximab, a CT abdomen revealed progression of liver disease. Therapy was switched to regorafenib. At the time of submission, she had completed 2 months of this treatment 30 months after initial diagnosis.

Discussion

Colorectal cancer is the third most common malignancy and the third most common cause of cancer death in the United States [1]. Brain metastasis occurs in approximately 1.5% of all colorectal cancer (CRC) cases, but this percentage is expected to increase as improving treatment options extend overall survival for patients with metastatic colorectal cancer (mCRC) [2-7]. Brain metastases are approximately three times more likely to arise from distal than proximal colon primary sites [8], partially owing to the distal anatomic overlap of portal and systemic circulation. CRC brain metastasis typically occurs in the setting of concurrent extra-cranial metastases, with liver, lung, and bone being the most common sites [2,3,5-7]. Brain metastasis in the absence of other extra-colonic locations is rare, occurring in less than 0.5% CRC cases. With respect to brain metastases, infra-tentorial lesions are observed in less than 20% of brain metastases from mCRC [2-7] (**Table 1**). Furthermore, the median time from diagnosis of CRC to brain metastasis occurrence has been reported to be between 22 and 36 months [9], unlike our case where brain metastasis represented the initial manifestation of metastatic CRC (mCRC). Thus, this case of mCRC originating from the proximal colon, presenting initially as an isolated, infra-tentorial, synchronous brain metastasis represents a particularly uncommon presentation of an otherwise common malignancy.

Prognosis is generally poor in patients with brain metastases in mCRC, with a median overall survival in the range of 5 months (range 4.5-7.4 months, **Table 1**). Neurosurgical resection of brain

Table 1 Tumor characteristics from selected studies with BM in mCRC, with references. BM: Brain metastasis; NR: not reported; WBRT: Whole brain radiation therapy; SRS: Stereotactic radiosurgery.

	Onodera et al. [3]	Nieder et al. [4]	Jung et al. [5]	Noura et al. [6]	Damiens et al. [7]
# Patients	17	35	126	29	48
Mean Age, years	59	63	62	58	63
Male:Female ratio	3.2	NR	1.8	3.8	1.1
Incidence of BM in CRC, %	1.6	NR	1.6	1.3	NR
Primary tumor site, %					
Ascending+transverse	0	NR	24	NR	40
Descending+sigmoid	29	NR	13	NR	12
Rectum	71	NR	63	59	48
BM characteristics, %					
Single	NR	49	40	31	63
Multiple	76	51	60	69	37
Supra-tentorial only	NR	NR	74	48	54
Infra-tentorial only	29	NR	18	6	23
Concurrent met site, %					
Lung	76	NR	72	69	64
Liver	47	NR	33	24	50
Lung+Liver	NR	NR	NR	NR	NR
Bone	23	NR	21	6.8	NR
None	12	34	8	21	10
Median survival after BM, months (range)					
Overall median survival	4.5 (NR)	5	5.4 (3.9-6.9)	7.4 (NR)	4 (1-13)
Surgery only	5.2* (NR)	NR	11.5** (0.2-22.7)	5.1 (NR)	3 (NR)
WBRT	4.5 (NR)	3 (1-8)	4 (1.4-6.5)	7.9 (NR)	4 (NR)
SRS	5.2* (NR)	NR	9.5 (4.7-14.2)	7 (NR)	NR
Surgery+Radiation	NR	9* (2-24)	11.5** (0.2-22.7)	11.4*** (NR)	13 (NR)
Supportive cares	3.7 (NR)	NR	1.5 (1.1-1.9)	1.6 (NR)	2 (NR)
Chemotherapy after BM	NR	NR	12.7 (9.5-16.0)	NR	NR NR

*Patients who received "surgery or radiosurgery" were combined into the same analysis group.

**Patients who received "surgery +/- WBRT" were combined into the same analysis group.

***Patients received surgery plus either WBRT or SRS.

metastasis followed by whole brain radiotherapy (WBRT) may improve survival by up to approximately 6 months in patients with mCRC, compared to either surgery or radiation alone [3-7,10-13]. Survival outcomes with various approaches to CRC brain metastases are listed in **Table 1**. Infratentorial metastasis has been shown to be a poor prognostic factor when compared

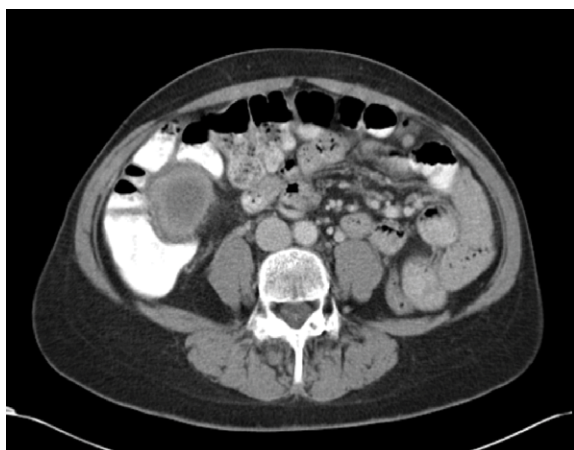


Figure 2 Representative image from the patient's abdominal CT demonstrating the centrally-necrotic right-sided colon mass. No radiographic evidence of liver or lung lesions was noted on this CT.

to supratentorial metastasis (5.1 vs 9.1 months). Other factors such as gender and number of metastases do not appear to impact overall survival after neurosurgical resection of brain metastasis [14].

Limited data exists on which systemic agents are optimal in the first-line treatment for CRC brain metastases [4,15-17]. The standard options include oxaliplatin or irinotecan combined with 5-fluorouracil/leucovorin plus a biologic agent targeting the vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) pathways. For those with RAS wild-type cancers, no data has been reported on the effectiveness of panitumumab or cetuximab in CRC brain metastases. The frequency of KRAS mutations among patients with CRC brain metastases has been reported at 56%, somewhat higher than the frequency of KRAS mutations reported for mCRC in general (40%) [18]. Since patients with KRAS mutations are not candidates for treatment with the EGFR antagonists cetuximab or panitumumab, these therapies may play less of a role in patient with CRC brain metastases [19].

Bevacizumab, a humanized monoclonal antibody with activity against vascular endothelial growth factor A ligand, has been approved as first and second-line therapy in mCRC when

combined with cytotoxic chemotherapy. However, the utility of this agent for treating brain metastases remains unclear, as an early case of intra-cerebral hemorrhage after bevacizumab administration led to the exclusion of patients with BM from virtually all subsequent clinical trials [20-23]. Importantly, in a 2008 case report, this complication was not observed in a patient with mCRC and known brain metastasis when bevacizumab was added to salvage 5-FU-based therapy [20]. Ongoing studies with gliomas and breast cancer are providing similar results, which may renew enthusiasm for more rigorous clinical investigation of bevacizumab and other targeted agents in the treatment of brain metastases in mCRC [23-25].

We present an uncommon case of isolated symptomatic infra-tentorial brain metastasis as the initial presentation of right-sided mCRC in an otherwise healthy 55 year-old female. Despite the usually poor prognosis associated with infra-tentorial brain metastasis in mCRC, she was alive and continuing palliative therapy 30 months after diagnosis. This case further highlights the benefit of combined versus single modality treatment for brain metastases in mCRC. The role of biologic agents in the treatment of brain metastases remains unclear, warranting further study in this patient population.

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