

Case Report

Multiple colonic epithelioid angiosarcoma: a case report and review of literature

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Abstract: Primary angiosarcoma of the large intestine is an extremely rare and aggressive malignancy. Epithelioid angiosarcoma (EAS) is a variant of angiosarcoma and tends to be deep-seated. Because of its rarity and morphological similarity, EAS may be misdiagnosed as poorly-differentiated carcinoma, especially in limited tissue biopsy. Here, a case of colonic EAS in a 77-year-old female presenting as melena is reported to define the clinicopathologic features of the rare disease with emphasis on differential diagnosis. By colonoscopy, multiple masses were found in the sigmoid and transverse colon. Histological examination showed epithelioid neoplastic cells with prominent nucleoli, which were morphologically similar to poorly-differentiated carcinoma. Immunohistochemical study revealed that the neoplastic cells were positive for both epithelial markers (AE1/AE3, CK7, and P63) and specific endothelial markers (CD31 and ERG). These results suggest that a panel of immune markers including endothelial markers should be used for differential diagnosis in colorectal epithelioid tumors.

Keywords: Angiosarcoma, epithelioid angiosarcoma, colorectal tumor, differential diagnosis

Introduction

Angiosarcoma is a rare and aggressive malignancy which often metastasizes to lymph node, lung, and bone at early stage. Angiosarcoma commonly occurs in subcutaneous soft tissue and primary colorectal angiosarcoma is extremely rare. Epithelioid angiosarcoma is a variant of angiosarcoma which is mainly composed of epithelioid neoplastic cells. Epithelioid angiosarcoma tends to be deep-seated. Colonic epithelioid angiosarcoma was first described by Saito in 1987 [1]. Angiosarcoma shows a wide morphologic spectrum, ranging from anastomosing vascular channels, bundles of spindle cells to solid epithelioid cells. Epithelioid angiosarcoma can express epithelial markers such as AE1/AE3, P63, which pose a potential diagnostic pitfall [2]. Colorectal epithelioid angiosarcoma may be easily misdiagnosed as poorly-differentiated adenocarcinoma or other epithelioid tumors without the aid of endothelial markers, especially in limited tissue biopsy.

Case report

A 77-year-old female was admitted by presenting with melena for three months. By colonoscopy, multiple protuberant dark red mucosal lesions were found in the sigmoid and transverse colon (**Figure 1A** and **1B**). Computed tomography scan and endoscopic examination of small intestine, stomach showed unremarkable findings. There was no previous history of malignancy or radiation exposure.

Routine blood test revealed decreased red blood cell count ($2.04 \times 10^{12}/L$ vs. $3.8-5.1 \times 10^{12}/L$ for normal) and a decreased hemoglobin content (58 g/L vs. 115-150 g/L for normal). Blood coagulation function assay showed an elevated level of D-dimer ($3000 \mu g/L$ vs. $0-550 \mu g/L$ for normal). The serum levels of tumor markers such as AFP, CEA, CA125, and CA199, were within the normal limit.

Specimens of colonic lesions were obtained by endoscopic mucosal resection technique (EMR)

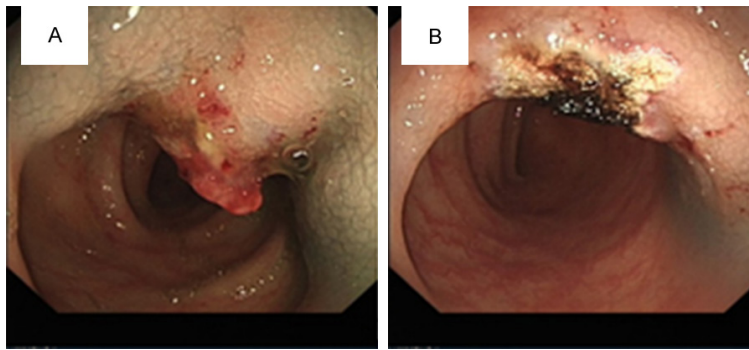


Figure 1. Gross appearance. A, B. Lesions of transverse colon and sigmoid colon.

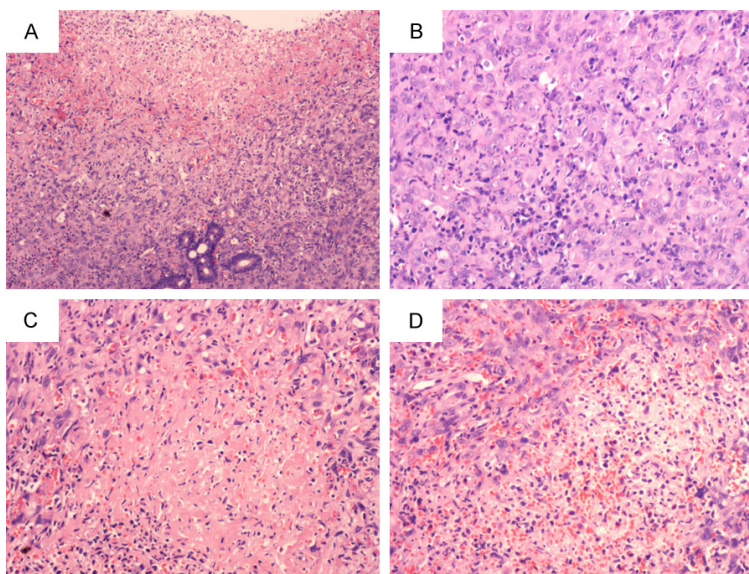


Figure 2. Histology. A. Mucosal ulceration was on the upper part of the lesion (H.E. $\times 100$). B. Solid sheets of epithelioid neoplastic cells with prominent nucleoli and intracytoplasmic lumina containing red blood cells were observed (H.E. $\times 200$). C, D. Necrosis and hemorrhage were found in the lesion (H.E. $\times 200$).

and used for pathological examination. Pathological diagnosis of epithelioid angiosarcoma was then made according to histological and immunohistochemical findings. Subsequent PET-CT (fluorodeoxyglucose positron-emission tomography/CT) scan showed remarkably increased FDG (fluorodeoxyglucose) metabolic activities in lymph nodes of bilateral pulmonary hilar region, mediastinal, and retroperitoneal location, as well as in bones of right humerus, right ilium, lumbar, left pubis, and left femur. Multiple metastatic lesions of lymph nodes and bones were considered according to PET-CT results.

about $0.8 \times 0.5 \times 0.4$ cm and $1.2 \times 0.5 \times 0.4$ cm in size, respectively. Microscopically, H.E sections of both sigmoid and transverse colon showed solid sheets of epithelioid neoplastic cells with prominent nucleoli. The tumor cells show abundant eosinophilic cytoplasm, which was very similar morphologically to undifferentiated carcinoma or poorly-differentiated adenocarcinoma (Figure 2A and 2B). Intracytoplasmic lumina containing red blood cells were easily observed (Figure 2B). Ulceration, necrosis, hemorrhage, and numerous mitotic figures can be found (Figure 2A, 2C and 2D). Infiltration of lymphocytes and plasmacytes was obvious.

Because of the high clinical stage of the disease, palliative therapy was chosen by the patient and her relatives. The patient passed away three months later.

Materials and methods

The tissue of colonic mass was fixed and paraffin-embed sections were made by routine procedure. Immunohistochemical staining was performed by the EnVision method. A panel of commercial antibodies (Products of Beijing Zhongshan Golden Bridge Biotechnology, Beijing, China) including AE1/AE3 (pan-Cytokeratin cocktail), CK8/18, CK20, EMA, P63, E-cadherin, CD31, CD34, ERG (avian v-ets erythroblastosis virus E26 oncogene homologue), CD56, SYN, CGA, Vimentin, D2-40, Calretinin, SMA, Desmin, CD117, DOG1, S100, HMB45, and CD45 (LCA, leukocyte common antigen), were used for immune phenotype study. Appropriate positive and negative controls were run concurrently for all the markers tested.

Results

Grossly, the mucosal lesions in the sigmoid and transverse colon were dark red color and

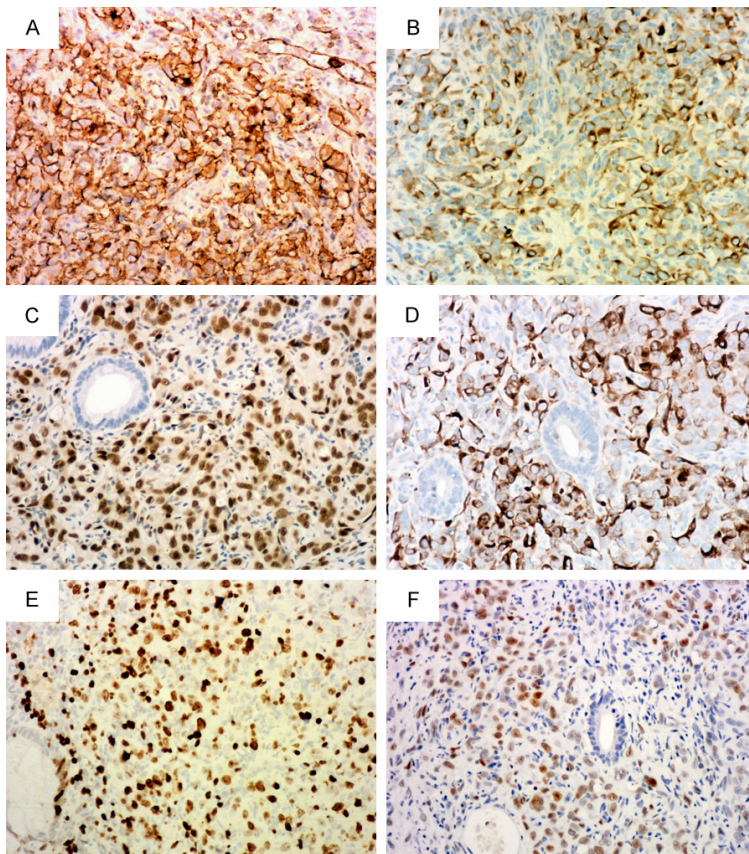


Figure 3. Immunohistochemistry. The neoplastic cells were positive for CD31 (A), CK-pan (B), CK7 (D), and nuclear positive for ERG (C) and P63 (F). Approximately 50% of the neoplastic cells were positive for Ki67 (E).

The Ki67 positive index of the neoplastic cells was nearly 50% (**Figure 3E**), which indicated a high proliferation activity.

Immunohistochemical analysis revealed that the neoplastic cells were positive for AE1/AE3, CK7, P63, CD31, ERG, and Vimentin, while negative for CD56, SYN, CGA, EMA, D2-40, CD34, Calretinin, SMA, Desmin, CD117, DOG1, S100, HMB45, and CD45 (**Figure 3**).

Discussion

Angiosarcoma accounts for less than 1% of all sarcomas. Epithelioid angiosarcoma is a rare subtype of angiosarcoma. To our knowledge, only 25 cases of colorectal angiosarcoma (including the current case) have been reported in the English literature so far (**Table 1**). Sigmoid colon was the most affected location (11/25, 44%), followed by rectum (7/25, 28%) and cecum (4/25, 16%). The median age was 63 years-old, while the ratio of male to female was

1:1.5 (10:15). More than half (11/21) died within one year and many of them (12/22) showed epithelioid morphology.

Epithelioid angiosarcoma mimics carcinoma morphologically and may express epithelial markers such as AE1/AE3, P63, which poses a significant diagnostic pitfall [2]. Moreover, epithelioid angiosarcoma displays solid sheet-like growth pattern and should be differentiated with other epithelioid tumors including other types of epithelioid vascular tumors, poorly-differentiated carcinoma, epithelioid gastrointestinal stromal tumor (GIST) [3], malignant mesothelioma, melanoma, large cell lymphoma and epithelioid variant of malignant peripheral nerve sheath tumor (MPNST), etc.

Initially, other epithelioid vascular tumors such as pseudo-myogenic hemangioendothelioma (PMH) and epithelioid hemangioendothelioma (EHE)

may also show epithelioid morphology, but their biological behavior and prognosis are quite different.

PMH is also called epithelioid sarcoma-like hemangioendothelioma due to its morphological similarity to epithelioid sarcoma [4]. PMH composed of relatively uniform plump, eosinophilic spindle cells with vesicular nuclei, despite focal epithelioid area may be present. The neoplastic cells of PMH arranged in fascicles and ill-defined nodules pattern and the neoplastic cells commonly lack prominent nuclear atypia and mitosis. PMH affects mainly adolescents or young adults with a male predominance and lacks metastatic potential.

EHE can virtually arise from any organ with a wide age range, although middle-aged adults are most affected [5]. EHEs of soft tissue are usually solitary, but tend to be multicentric at other sites. EHEs are often vasulocentric and the tumor cells are usually arranged in cords or

Colonic epithelioid angiosarcoma

Table 1. Reported colorectal angiosarcoma in literature

S/A	Location	Size (cm)	Met./Inv.	Pathology (E/S)	Phenotype	Follow-up	Author, Year
F/77	Sigmoid, transverse	0.8~1.2	LN, lung, bone Met.	E	CD31+, ERG+, CK7+, P63+	DOD in 3 Mo	Current, 2016
F/63	Sigmoid	10	Margin+	S	CD31+; CK7-, CK20-, pCK-	Multiple Met. in 3 Mo	Keyser [11], 2015
M/72	Colon	NA	NA	E	pCK-, CD31+; CD34-, CK7-	DOD in 12 Mo	Wu [12], 2015
F/69	Ascending	NA	Brain, adrenal, lung	S	CD31+, D34+	Alive after 5 Mo	Sherid [13], 2013
F/68	Rectum	3.4	Regional LN, liver Met.	E	CD31+, D34+	DOD in 2 Mo	Sherid [13], 2013
M/40	Sigmoid	1.5	NA	E	CD31+, F8+ AE1/AE3+, CAM5.2+	Alive 24 Mo with bone Met.	Betteddini [14], 2013
F/21	Sigmoid	9	No	S	CD31+; AE1/AE3-	NSD for 3 yr	Lo [15], 2011
F/85	Cecum	2	No	E	CD31+; CD34-	NSD for 2 yr	Pascual [16], 2010
M/49	Rectum	NA	Multiple organ Met.	S+E	CD31+, D34+	DOD after 10 Mo	Tardio [17], 2009
M/74	Rectum	8	No	E	CD31+, D34+	NA	Ahmad [18], 2008
F/60	Sigmoid	6.5	Thoracic, bone Met.	NA	CD34+, F8+	DOD in 4 Mo	Chaar [19], 2007
M/63	Sigmoid	Large	Multiple organ Met.	E	CD31+	DOD in 1 Mo	Cammarota [20], 2006
M/42	Rectum	2.5	Neck LN, regional LN	E	NA	NA	Hinterseher [21], 2005
M/17	Sigmoid	12	No	S	CD31+, CD34+	NSD for 19 Mo	Komorowski [22], 2004
M/70	Rectum	4.5	LN Inv.	S	CD31+, CD34+	DOD in 6 Mo	Brown [23], 2004
F/32	Rectum	1~2.8	No	E	CD31+, CD34+, pCK+, CK7-, CK20-	NSD in 27 Mo	Allison [24], 2004
M/55	Cecum	2.5	Regional LN Met.	NA	NA	Alive 13 Mo NSD	Rozario [25], 1995
F/70	Sigmoid	30	No	E	AE1+; AE3-	NSD for 2 yr	Watanabe [26], 1993
F/70	Rectum	5	Vertebral Met.	S	F8+, UEA-1+; pCK-	DOD in 2 Mo	Ben-Izhak [27], 1992
F/80	Sigmoid	NA	Small bowel, Intra-abdominal Met.	NA	NA	DOD in 2 Weeks	Wolov [28], 1991
F/16	Sigmoid	3.5	No	S	F8+	NSD for 3 yr	Smith [29], 1990
F/57	Cecum	6	NA	S	F8+	DOD in 4 Mo	Taxy [30], 1988
F/59	Cecum	NA	Multiple organ Met.	NA	NA	NA	Joseph [31], 1987
M/72	Descend	10	LN Met.	E	a1-antitrypsin+	DOD in 4 Mo	Saito [1], 1987
F/46	Sigmoid	3.5	No	S	NA	NSD for 21 Mo	Steiner [32], 1949

S/A: sex/age; F: female; M: male; Met./Inv: metastasis/Invasion; No: no sign of metastasis; E/S: epithelioid/spindle morphology; NSD: no sign of disease; DOD: dead of disease; NA: Data not available; Mo: month(s); yr: years; VM: vimentin; pCK: Pan-Cytokeratin or AE1/AE3.

small nests which were surrounded by variable amount of hyaline or myxoid stroma. Prominent cytoplasmic vacuoles containing erythrocytes are frequently observed. The tumor cells display mildly to moderate atypia. The designation of malignant epithelioid hemangioendothelioma refers to more aggressive subtype of EHE, although the distinction between malignant epithelioid hemangioendothelioma and epithelioid angiosarcoma is not well defined. Generally, malignant epithelioid hemangioendotheliomas may show histological characteristics of typical epithelioid hemangioendothelioma accompanied with larger nests of cells with prominent cytologic atypia and high mitotic activities or even areas indistinguishable from epithelioid angiosarcoma. Large tumor size (more than 3 cm) and mitotic activity (more than 3 mitotic figures/50 high power fields) are associated with higher mortality [6].

Second, epithelioid angiosarcoma should differentiate from poorly-differentiated carcinoma. Epithelioid angiosarcoma mimics poorly-differentiated carcinoma or metastatic carcinoma by both morphology and immune phenotype. The presence of cytoplasmic vacuoles and lack of desmoplastic reaction are helpful in distinguishing epithelioid angiosarcoma from primary or metastatic carcinoma of colon. Epithelioid angiosarcoma may be positive for epithelial markers such as AE1/AE3, CK7, and CK8/18. In the present case, the neoplastic cells were positive for AE1/AE3, P63, and CK7, while the endothelial nature of the neoplastic cells was identified by sensitive and specific endothelial markers CD31 and ERG [7, 8]. Although the majority of carcinomas are negative for vascular markers of CD31, a few cases of metastatic carcinoma have been reported to be positive for CD31 [9]. It has been suggested that more than one endothelial marker, especially CD31 and ERG, should be used for differential diagnosis of epithelioid angiosarcoma.

Interestingly, neoplastic cells in present case were also positive for P63, which is commonly regarded as a marker for squamous epithelia, basal, and myoepithelial cells and their corresponding malignancy. A previous study suggested that P63 can be expressed in about 24% of malignant vascular tumors other than Kaposi sarcoma [10].

Third, epithelioid angiosarcoma should differentiate from epithelioid type of gastrointestinal

stroma tumor (GIST). It has been reported that about 50~60% cases of angiosarcoma are Kit-positive and lack the mutation of exon11 and exon17 of c-kit [3]. Angiosarcoma may be positive for both CD34 and CD117 (Kit), which was regarded as markers of GIST. Because of its rarity, colorectal epithelioid angiosarcoma may be misdiagnosed as epithelioid GIST and lead to serious clinical consequences [3].

In addition, colorectal epithelioid angiosarcoma may contain local area of granulation tissue and should not be confused with granulation tissue of a mucosa ulcer, especially in limited tissue biopsy. Other tumors such as epithelioid malignant mesothelioma, melanoma, large cell lymphoma, and epithelioid variant of MPNST, can be similar to epithelioid angiosarcoma morphologically and immunohistochemistry is crucial for differential diagnosis.

Clinically, gastrointestinal bleeding and anemia are common symptoms due to mucosal ulcer and necrosis for patients of colorectal angiosarcoma. Surgery alone or surgery combined with adjuvant chemotherapy or radiotherapy has been used for treatment of colorectal angiosarcoma, but the effects remain to be evaluated [5].

The general prognosis of colorectal angiosarcoma was very poor. Many cases have a very aggressive clinical course with the development of systemic metastasis within one year after diagnosis.

In summary, we reported a rare case of colonic epithelioid angiosarcoma which should differentiate from poorly-differentiated carcinoma and other epithelioid tumor. For correct diagnosis of poorly-differentiated epithelioid tumor, a panel of immune markers including endothelial markers should be used.

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Disclosure of conflict of interest

None.

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