Primary Colonic Angiosarcoma Seen in a Patient on Calcium Channel Blocker: A Case Report with Summary Analysis of 32 Other Cases from the Literature

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Patient: Female, 54
Final Diagnosis: Primary colonic angiosarcoma
Symptoms: Rectal bleeding
Medication: Levamlodipine Besylate
Clinical Procedure: Hemicolectomy
Specialty: Gastroenterology and Hepatology

Objective: Rare co-existence of disease or pathology
Background: Angiosarcoma is a rare malignant mesenchymal tumor of vascular endothelial cell origin. Its occurrence in the colorectal region is extremely rare. Only 32 cases of primary colorectal angiosarcoma are reported in the current literature. Angiosarcoma in association with calcium channel blocker has been rarely reported. We present such a case of a patient who had been on levamlodipine besylate, a calcium channel blocker, for over 10 years.

Case Report: A 53-year-old female with hypertension presented with a fever, a dry cough, and hematochezia. Computed tomography (CT) scan and angiography demonstrated a 6-cm vascular mass in the ileocecal region. The clinical symptoms stopped soon after a right hemicolectomy. The histopathology with immunohistochemical studies confirmed the diagnosis of angiosarcoma. Three months after surgery, the patient had evidence of recurrence of the tumor, however, she no longer presented with a fever or a dry cough. The patient was receiving chemotherapy at the time of the report.

Conclusions: Colorectal angiosarcoma is a rare malignancy of endothelial origin with uncertain etiology and often has a poor prognosis. Angiosarcoma seen in a patient taking calcium channel blocker is rare but alarming. CT scan and angiography are helpful tools to raise the suspicion of the diagnosis. A definitive pathological diagnosis relies on histopathology with immunohistochemical stains of endothelial markers. Surgical resection is still the best choice of the different treatment options.

MeSH Keywords: Angiography • Calcium Channel Blockers • Colorectal Neoplasms • Hemangiosarcoma • Immunohistochemistry

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Background

Angiosarcoma is an uncommon type of highly malignant sarcoma that has vascular endothelial cell origin. It accounts for less than 1% of all soft tissue sarcomas. It is commonly seen in the skin and soft tissue. Its occurrence in the gastrointestinal (GI) tract is extremely rare [1–47], highly invasive and often metastasizes rapidly. Thus, it generally carries a poor prognosis unless it is recognized early and treated properly. The etiology of angiosarcoma is uncertain [2,7,8,18,19,22,40,42,43]. Angiosarcoma has been rarely reported in a patient who takes calcium channel blocker to control blood pressure [48,49]. We report such a case along with a summary analysis of 32 published primary angiosarcoma cases in terms of patient’s age/sex, potential etiology, clinical presentations, radiology, pathology, and prognostic data.

Case Report

A 54-year-old Chinese female was admitted to the Second Hospital of Shanxi Medical University (PR China) in April of 2016, with chief complaints of an intermittent fever between 37.5°C and 38.2°C and a dry cough for three months as well as a progressively worsening dark red jelly-like stool and weight loss for one month. Past medical history was significant for 10 years of hypertension controlled by levamisodine besylate, a calcium channel blocker. Physical examination was remarkable for a painless, firm, non-mobile mass identified in the right lower quadrant of the abdomen. Relevant ancillary test findings included lower hemoglobin of 10.3 g/dL, positive fecal occult blood, high erythrocyte sedimentation rate (ESR) of 80 mm/hour and C-reactive protein of 17.6 mg/dL; tests were negative for fever-filtering tests, thyroid function tests, and tumor markers (CA19-9, NSE, CEA, SCC, β-HCG, AFP, CA72-4, c-PSA, CA125, CA153, CK19, CA242). Chest CT was unremarkable. Abdominal CT with contrast showed a septated hypodense mass (Figure 1A). Tumor association with a visible vascular network was shown in angiography (Figures 1B). Vascular surgery exploration revealed a well-defined tumor in the ileocecal region with numerous blood vessels visible on the surface and significant ileocecal-appendix-mesangial adhesion. Complete resection of the tumor (Figure 1C) with right colectomy and the ileocolic anastomosis was performed. Gross pathological examination of the tumor showed a reddish-tan gray cut surface. Microscopy examination with hematoxylin and eosin (H&E) stained slides revealed a malignant vascular spindle cell tumor associated with necrosis and hemorrhage. Many small to medium-sized blood vessels embedded in a sea of numerous atypical spindle cells were seen under low-power view. The high-power features were seen in Figure 1D.

Immunohistochemistry stains demonstrated that the tumor cells were positive for CD34 (Figure 1E), FVIII (Figure 1F), CD31, Vimentin, Fli1, CD117 (rare), S-100 (rare), and cytokeratin (rare), but were negative for smooth muscle actin (SMA), desmin, epithelial membrane antigen (EMA), D2–40, and DOG-1. The proliferation index by Ki67 was 20%. The final pathological diagnosis was colonic angiosarcoma involving the serosal surface and lymph nodes.

The patient’s clinical symptoms subsided and dissipated after the surgery. The patient had persistent abdominal pain and was diagnosed with local tumor recurrence, 70 days post-operation. However, no fever, dry cough, or jelly-like stools were noted at the time of the recurrence. The patient had been undergoing chemotherapy.

Discussion

Angiosarcoma, also known as malignant hemangiendothelioma, is a highly malignant soft tissue sarcoma, which originates from vascular endothelial cells. It accounts for less than 1% of soft tissue sarcoma [1]. It often occurs in the skin, subcutaneous tissue, muscle, and bone, but is also seen in the oral cavity, mediastinum, and retroperitoneum. Angiosarcoma in the digestive system is relatively rare and the presence of solid organs such as the liver and spleen are common. It is especially rare to see angiosarcoma in the gastrointestinal tract. Within the gastrointestinal tract, angiosarcoma is more likely to be seen in the stomach and small intestine [40]. Colorectal angiosarcoma is extremely rare. There are less than 40 cases reported in the world. We found 39 such cases, in addition to the current patient. Among them, six patients (17%) have angiosarcoma that metastasized to the colorectal region. Our patient was found to have no other lesions except the mass described in this report. Thus, the diagnosis was determined to be primary colonic angiosarcoma. Here we perform a summary analysis focusing on these 33 cases of primary colorectal angiosarcoma (Tables 1) and discuss the related issues.

The mean age of colorectal primary angiosarcoma was 56 years (range of 16 to 85 years); 64% of patients were over the age of 50 years. It occurred in males and females equally. The etiology of angiosarcoma was considered uncertain. It might be associated with long-term exposure to arsenic, vinyl chloride, thiorium oxide, and other chemicals. Chemotherapy and chronic lymphedema may also be associated with angiosarcoma. Angiosarcoma can be located around an arteriovenous fistula or an area where persistent foreign substances are located [18,22,40,42,43]. Among the 33 primary colorectal angiosarcoma cases analyzed, 12% had a history of radiation exposure [2,7,8,19]. Radiation exposure for these patients was noted at the time of the recurrence. The patient was found to have no other lesions except the mass described in this report. Thus, the diagnosis was determined to be primary colonic angiosarcoma. Here we perform a summary analysis focusing on these 33 cases of primary colorectal angiosarcoma (Tables 1) and discuss the related issues.

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Figure 1. (A) Sagittal view of abdominal and pelvic CT with contrast enhancement. Arrow points to the mass. (B) Angiography, arrow points to the tumor mass. (C) Surgically resected fresh tumor. (D) High power view of H&E stained photo micrograph of angiosarcoma showing numerous small sized (curve arrows) and occasional medium sized (arrow) blood vessels formed by malignant endothelial cells (magnification 200×). (E) Immunohistochemistry CD34 (+) in malignant endothelial cells (200×). (F) Immunohistochemistry F-VIII (+) in malignant endothelial cells (200×).
Table 1. Summary analysis of 33 case reports of primary colorectal angiosarcoma.

| Analytic variables                             | Summary of analysis (N=33)                                                                 |
|------------------------------------------------|-------------------------------------------------------------------------------------------|
| Age (years)                                    | Mean=56 (range 16–85) Over 50 years of age: 21/33=64%                                      |
| Sex                                            | Female: 16/32=50% Male=16/32=50% Not reported=1                                               |
| Possible etiology related history              | Radiation: 4/33=12% Foreign body: 1/33=3% Chronic inflammation: 1/33=3% Other special event: 2/33=6% 1 renal transplant |
| Time from exposure to disease                  | Not reported: n=26 With records: n=7 Mean=18 years Range: 4 to 30 years                     |
| Clinical symptoms                              | Gastrointestinal bleeding: 22/33=67% Abdominal or perianal pain: 15/33=46% Bowel obstruction: 8/33=24% |
| Time from onsite to medical care               | With records: n=21 Mean=101 days Range: 1 day to 600 days                                |
| Physical signs                                 | Abdominal mass: 6/33=18% Paleness or anemia: 14/33=42%                                    |
| Tumor location                                 | Sigmoid colon: 12/33=36% Anorectal: 11/33=33% Cecum: 7/33=21% Ascending colon: 3/33=9% |
| Tumor gross appearance                         | Transverse and descending colon: 1/33=3% Polypoid/mass/obstructive: 6/24=25%              |
| Size of the tumor                              | Tumor size reported: n=27 Mean=5 cm Range: 1.5 cm to 12 cm                               |
| Pathological differentiation                  | "Malignant": 7/17=41% Well-diff: 5/17=29% Poorly diff.: 3/17=18% Well to poorly diff.: 2/17=12% |
| Histological type                              | Epithelioid: 11/21=52% Spindle: 6/21=29% Mixed spindle & epithelioid: 4/21=19%            |
| IHC                                            | CD31 Positive: 19/22=86% CD34 Positive: 12/15=80% FVIII Positive: 12/14=86%               |
| Metastasis                                     | Yes: 25/33=76% No: 8/33=24%                                                               |
| Follow-up                                      | Died: 17/29=59% Alive: 12/29=41% Not reported: n=4                                         |
long-term hemodialysis, and chronic colorectal ulcers were also reported (one case in each category). The average period from these exposures to the diagnosis of angiosarcoma was 18 years (range of 4 to 30 years). Our patient did not have any of these aforementioned medical histories except a history of long-term use of a calcium channel blocker to control her blood pressure. Angiosarcoma has also been reported in patients who take calcium channel blockers [48,49]. Our patient used levaldipine (also known as levoamlodipine or S-amlodipine; a calcium channel blocker that is a pharmacologically active enantiomer of amlodipine). Although the direct relationship between calcium channel blockers and angiosarcoma is not well established, it is very interesting to note the possibility of an association.

The main clinical manifestation of primary colorectal angiosarcoma in the published literature was gastrointestinal bleeding (67%). The second most common symptom was an abdominal/anal pain (46%). Other symptoms were intestinal obstruction (24%), diarrhea (15%), and weight loss (18%) (Table 1). These clinical manifestations were non-specific and could be easily confused with other diseases of the gastrointestinal tract, which would thus delay the diagnosis. Our patient presented primarily with gastrointestinal bleeding, diarrhea, and weight loss, which was consistent with previous literature. Interestingly, this patient also had a fever and dry cough with an unknown source of infection, no evidence of lung disease, unresponsiveness to antibiotic treatment, and her symptoms disappeared post-surgery. These clinical presentations were intriguing. Although fever has not been previously reported in primary colorectal angiosarcoma, it has been reported in splenic angiosarcoma [50,51]. Similar to our case, both of these splenic cases showed hemorrhage and necrosis. Since fever can be induced by tumor necrosis factor [52], it is reasonable to believe that our patient’s fever symptom was likely related to tumor necrosis. This justifies why the fever stopped after resection of the necrotic tumor. The etiology of the unusual symptom of a dry cough remains open for an explanation and justification. Although a dry cough can be one of the side effects of taking a blood pressure medication such as an angiotensin-converting enzyme (ACE) inhibitor, the medication our patient took to control her blood pressure was not an ACE inhibitor. It is interesting that a dry cough stopped after surgical resection of the angiosarcoma, but did not reappear after the tumor recurrence. It is also interesting to note that the tumor recurrence was not accompanied by the other primary symptoms of GI bleeding, diarrhea, and weight loss. The radiological sign of intestinal obstruction was compatible with the assumption that the recurrence tumor is extra-luminal. Since the tumor recurrence was not associated with GI bleeding or the uncommon symptoms of a dry cough and fever, it was reasonable to assume that the recurrent tumor was not exposed to the intestinal lumen where bacteria might have served as a co-factor to produce tumor-related factors that might cause a dry cough and fever. The authors propose that it is possible that there was/were mimic(s) of ACE inhibitor(s) produced by angiosarcoma itself that might have induce an ACE inhibitor-like-effect of a dry cough. The production of such mimic(s) or factor(s) might require the participation of GI flora. Regardless of the potential causes of a fever and dry cough, it is important for readers to remember these symptoms can be seen in primary angiosarcoma of the colon. However, one may wonder why a fever and dry cough were not reported in other published case reports of primary angiosarcoma. The authors suspect that these symptoms might have been seen as non-specific or unrelated and thus were not reported. The same reason might also explain why other reports of primary colorectal angiosarcoma have not mention the association with calcium channel blocker.

The average period from patient symptoms to medical treatment was 101 days (range of 1 day to 600 days/20 months). It took approximately four months from the initial appearance of a dry cough, fever, and other GI-related non-specific symptoms, to lead to the diagnosis for our patient. If a dry cough and fever were identified as being possible associations with potential angiosarcoma earlier, it would have likely resulted in the patient being treated sooner.

Diagnosis of angiosarcoma mainly depends on a combination of physical examination, imaging, and pathology. Currently, no reliable laboratory test can be used as a diagnostic tool for angiosarcoma [41]. Abdominal tenderness, abdominal masses (18%), pale skin/anemia (42%), and other signs can be seen upon physical examination. Our patient’s abdominal mass was first found by physical examination and confirmed by a CT with contrast.

The frequency of occurrence of angiosarcoma based on the current literature analysis was 36% in the sigmoid colon, 33.3% in the anorectal region, 21.2% in the cecum, 9.1% in ascending colon, and 3.0% in the transverse and descending colon.

In general, under endoscopy, an angiosarcoma grossly appears to be nodular or polyloid, mostly solid with a spongy part, diffuse or ulcerated, small or massive, and as a mostly locally organized firm mass. The invasive part can be soft, purple in destructive growth pattern, and associated with bleeding, necrosis, and a “fish-flesh” cut surface [41,43,46]. Among 24 cases with the tumor gross appearance reported, 75% (18/24) of these cases presented with tumor ulceration, hemorrhage, necrosis, and evidence of invasion, while 25% (6/24) of these cases were described as a polypoid mass with obstructive symptoms.

Based on 27 cases with tumor sizes reported, the mean was 5 cm, ranging from 1.5 cm to 12 cm. There were two cases...
reported as “large”. Tumor sizes were not reported for the remaining four cases. Tumor size and patient age have been proposed as important prognostic factors. Tumor sizes less than 5 cm and young patients both showed better prognosis [1,2]. Other factors that may significantly affect the prognosis include general condition of patient and metastatic status.

On a CT scan, angiosarcoma can be single or multiple, round or ovoid, and present as an irregularly poorly defined soft tissue mass with high density and intratumoral hemorrhage. It may be associated with liquefaction necrosis, cystic fibrosis or grid-like calcification. Due to its abundant tumor blood vessels, a CT scan with contrast shows incremental inhomogeneous enhancement in the arterial phase and decreasing yet persistent enhancement in venous and delayed phases. This feature should be differentiated from that seen in other vascular abnormalities such as an arteriovenous fistula, aneurysm, or other soft tissue sarcomas [42–44]. An arteriovenous fistula has different CT findings in different parts of the body. The main feature of arteriovenous fistula is abnormal dynamic channels that appear between the arterial and the venous phases. Proximal artery distortion, increased numbers, disorganization, angiomatoid or plaque-like appearance, as well as marked and persistent enhancement in venous and delayed phases, may also be seen in an arteriovenous fistula. However, low density is not seen within the tumor [45]. An aneurysm shows tumor-like expansion with enhancement matched with the narrowed lumen and often associated with thrombosis. Malignant soft tissue tumors with rich blood supplies often not only show copious irregular peritumoral angiogenesis but also show traffic and an arteriovenous vascular pool, which indicates its abundance of blood vessels or tumor vasculature and is not indicative of angiosarcoma. In general, it is the combination of a patient’s CT scan and angiography performance that leads to the radiological diagnosis of angiosarcoma.

Histopathologic examination with immunohistochemical stains may confirm the diagnosis of primary angiosarcoma [42,43]. Microscopically, the tumor generally contains enlarged spindle or irregular cells with nuclear atypia, frequent mitoses, prominent nucleoli, and abundant eosinophilic cytoplasm. Tumor cells may form diffuse or focally variable sized/shaped lumen structures. Hyperplastic vasculature may have both increased numbers and layers of endothelial cells. Some even show a papillary growth pattern. The differentiation of the tumor varies from non-tumor vascular lesions to well-differentiated tumor cavitory blood vessels. One of the most significant diagnostic features of the tumor is irregular shaped anastomosing vasculature with atypical endothelial cells that are filled with red blood cells [1,2,40–43]. Among 17 cases with pathological differentiation reported, 41% reported as malignant; 29% as well-differentiated; 18% as poorly differentiated; and 12% as well to poorly differentiated.

Immunohistochemistry with blood vessel/endothelial/epithelial markers can be used in the diagnosis of angiosarcoma. These markers include factor VIII (FVIII), UEA-1, CD34, CD31, CD117, vimentin, cytokeratin (CK), perivascular smooth muscle actin (SMA), EMA, and S100. FVIII is highly specific for the diagnosis of angiosarcoma, but the sensitivity for poorly differentiated angiosarcoma is not high [40]. UEA-1 has good sensitivity but low specificity [41]. CD34 is expressed higher in visceral angiosarcoma in contrast to CD34 expression in angiosarcoma of the skin. CD31 has better sensitivity than FVIII and higher specificity than UEA-1 [40]. CD117 is not commonly used as a vascular marker, but when it is positive, patients can be treated with imatinib therapy, which may be effective [2]. Among these vascular markers; CD31, CD34, and FVIII are commonly used. Our meta-analysis of the available data shows that the frequency of positive results for CD31, CD34, and FVIII is 86%, 80%, and 86%, respectively. Usually, a positive finding of one or more vascular markers along with a negative finding of epithelial markers can be diagnostic for angiosarcoma [43]. However, for epithelioid angiosarcoma, some epithelial markers can also be positive [12,40]. Differential diagnosis of angiosarcoma includes the following: for leiomyosarcoma, the cells are larger microscopically with significant nuclear pleomorphism and frequent mitosis. Myogenic markers such as desmin, actin, SMA should also be helpful. GI stromal tumors (GIST) may have spindle cells, epithelioid cells, or a mixture of both diagnostic features. CD117 (KIT protein) is positive in GIST with high sensitivity and specificity. CD34 can also be positive in GIST but has low specificity. For poorly differentiated metastatic carcinoma, microscopically shows more nuclear pleomorphism, more frequent abnormal mitosis, and virtually unnoticeable vascular structures. Immunohistochemically the tumor cells should express CK, but not express the vascular markers. Whereas, epithelioid sarcoma and malignant mesothelioma sometimes produce false vascular tumor-like morphology, can express vimentin and cytokeratin, but FVIII, CD34, and CD31 should be negative. For epithelioid hemangioendothelioma, the endothelial cells can be round, more polygonal or short spindle-shaped, and often grow in an endovascular pattern or adhere to the vessel wall. The nucleus is less pleomorphic and has less mitotic figures. Vascular markers can be positive but B72.3 is negative, which is a marker for adenocarcinoma. For Kaposi sarcoma, reticular fibers surrounding the tumor without vascular anastomosis chamber are formed, which is usually associated with immunosuppression such as AIDS. Kaposi sarcoma in the gut is often multifocal. For malignant melanoma, microscopically the tumor cells often have nests without significant vascular structure, express S100, and HMB45, and often show the formation of melanin. Pathological diagnosis of angiosarcoma in our patient is based on the immunohistochemical positivity of CD31, CD34, and FVIII, along with other supporting evidence.
Angiosarcoma is a highly aggressive tumor that metastasizes (76%) rapidly and shows a poor prognosis. Commonly seen metastatic sites include the regional lymph nodes (27%), bone (21%), lung (18%), liver (18%), and pelvis (9%). Other sites include the adrenal gland (6%), neck lymph nodes (6%), bladder (6%), brain (3%), spleen (3%), duodenum (3%), and uterus (3%). Our patient had local recurrence at the time of this report.

From our literature review we found follow-up periods ranged from two weeks to four years; with 41% of patients still alive at follow-up. Among the patients who died (59%), the median survival time was 4.5 months (range from two weeks to four years). It is unknown if a patient could survive more than four years.

The most effective treatment for angiosarcoma is still complete surgical resection of the tumor. Angiosarcoma is generally not sensitive to chemotherapy. However, for chemotherapy-sensitive tumors, adjuvant chemotherapy or post-surgical chemotherapy can be used. Commonly used chemotherapy includes doxorubicin, paclitaxel, mitomycin, iso-cyclophosphamide, epirubicin, docetaxel, etc. However, their actual benefits are unclear. In addition, blood angiography embolization can be considered for preoperative preparation and treatment. Biological therapy, and specifically anti-neovascular therapy, such as afatinib mesylate, can also be used.

Overall, colorectal angiosarcoma is a rare malignant tumor with poor prognosis. Early recognition of the clinical signs and symptoms with early diagnosis and complete surgical resection should be beneficial. Certain chemotherapy and biological therapy may play an important role in treating angiosarcoma. Further investigation of the pathophysiology of angiosarcoma in the GI tract may help future patient management.

Conclusions

Colorectal angiosarcoma is a rare but aggressive malignancy of endothelial origin. It is interesting and alarming to note that angiosarcoma may be related to a long-term usage of calcium channel blocker. CT scan and angiography are helpful to raise the suspicion of the diagnosis. A definitive pathological diagnosis relies on histopathology with immunohistochemical stains of endothelial markers. Surgical resection is still the best choice of the different treatment options.

Conflict of Interest

None.

References:

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