

The poor prognosis of the primary gastric epithelioid angiosarcoma

A case report

Jie Xia, MD, DiKe Shi, PhD, ZhiWei Wu, MD, Yang Chen, MD, BaoQing Liu, MD, Li Chen, PhD, Wongkamchai Metta, MD, YiXiong Zheng, PhD*

Abstract

Rationale: Primary gastric epithelioid angiosarcoma is a highly aggressive endothelial cell malignancy and may pose a great diagnostic challenge.

Patient concerns: Here we describe the case of a 56-year-old man presented with melena and epigastric dull pain for 2 weeks.

Diagnosis: Primary gastric epithelioid angiosarcomas: the definitive diagnosis was provided by immunohistochemical analysis with endothelial markers such as cluster of differentiation 31 (CD31), ether-a-go-go-related gene (ERG), and Freund leukemia integration (FLI-1).

Interventions: After gastroscopic biopsy was performed at the bleeding fundus and the results suggested malignant tumor, radical gastrectomy was performed.

Outcomes: Unfortunately, regional lymph node enlargement and distant metastases occurred about 1 month later. The patient did not have the opportunity to undergo chemotherapy or other treatment and died from multiple organ dysfunction syndrome.

Lessons: Primary gastric epithelioid angiosarcomas are rare tumors with a high rate of lymph nodes and peripheral organs metastasis. The strong cytokeratin expression in epithelioid angiosarcomas represents a diagnostic pitfall for pathologists. Their clinical behaviors are unpredictable and results with surgical excision alone have been disappointing. Thus, the prognosis is generally considered poor and patients seldom can survive over 1 year after diagnosis.

Abbreviations: AS = angiosarcomas, CD = cluster of differentiation, CK = cytokeratin, CT = computed tomography, EAS = epithelioid angiosarcomas, EMA = ethylene maleic anhydride, ERG = ether-a-go-go-related gene, ETS = E-twenty-six, FLI-1 = Freund leukemia integration 1, Hb = hemoglobin, MODS = multiple organ dysfunction syndrome, MRI = magnetic resonance imaging, PD-L1 = programmed cell death 1 ligand 1, UEA-1 = ulex europaeus agglutinin-1.

Keywords: epithelioid angiosarcoma, immunohistochemistry, prognosis, stomach

1. Introduction

Angiosarcoma (AS) is one of the most aggressive tumors which originates from vascular or lymphatic endothelial cells. These tumors account for <1% of all soft tissue sarcomas, most

frequently occur in the skin and subcutis.^[1] However, some of them arise in those well-recognized organs such as breast, small intestine, spleen and a few cases develop at the site of previous therapeutic radiation or chronic lymphoedema. Angiosarcomas can be classified into well-differentiated, poorly differentiated, and epithelioid tumors. In contrast to these common features, epithelioid angiosarcoma is known as a unique morphologic subtype of angiosarcomas, in which the malignant endothelial cells have a predominantly epithelioid appearance.^[2] Histologic diagnosis of gastric epithelioid angiosarcomas have always been challenging for pathologists. To the best of our knowledge, few cases of primary angiosarcomas of stomach have been reported in the English literature. Because of the rarity of epithelioid angiosarcomas, optimal management has not been defined. Thus, such a well-documented epithelioid angiosarcoma of the stomach is described. The aim of this study is to raise awareness of this rare and highly aggressive neoplasm and differentiate it from poorly differentiated adenocarcinoma, metastatic carcinomas, epithelioid sarcoma, epithelioid leiomyosarcoma, and so on.

2. Case report

A 56-year-old man was referred to the gastrointestinal department with complaints of 2-weeks history of melena and epigastric dull pain. No mucous stool, no bowel habits change was present

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JX and DKS equally contributed to this study.

Ethical Approval: This study was approved by the Ethics Committee of Second Affiliated Hospital of Zhejiang University. Written informed consent was obtained from the patient and patients' guardians.

The authors have no conflicts of interest to disclose.

Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China.

* Correspondence: YiXiong Zheng, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China (e-mail: 2100011@zju.edu.cn).

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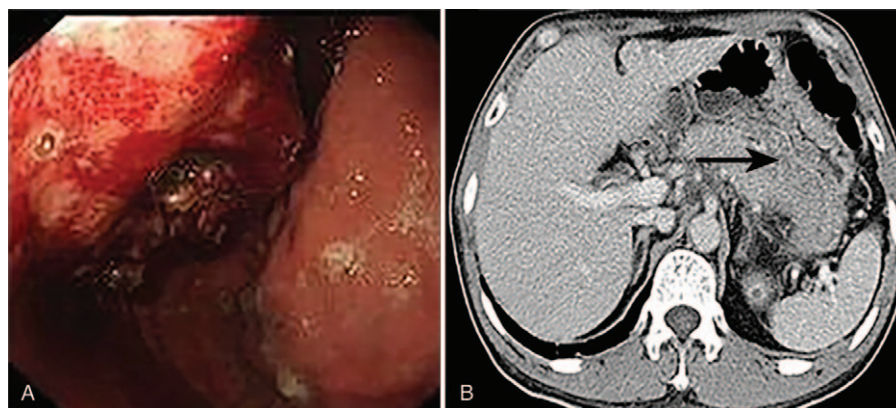


Figure 1. Endoscopic view of a bulky mass in the fundus of stomach (A). Abdominal computed tomography showed a tumor was located in the fundus of the stomach, invading the pancreas (B) (arrow).

and he denied fever, nausea, or vomiting. Meanwhile, the patient's medical and family histories were normal. Physical examination revealed there was no anemia or enlarged lymph nodes such as Virchow lymph nodes. For laboratory tests, occult blood test of stool was positive. Hematological test revealed a normal level of hemoglobin (Hb), 130 g/L. Peripheral blood tumor markers were within the normal range too. Endoscopic examination showed erosive hemorrhage on the surface of the tumor with a diameter of about 7 cm (Fig. 1A). A biopsy of this area exhibited malignant tumor. Abdominal computed tomography (CT) showed a bulky mass with ulceration, located in the fundus of the stomach and marked thickening of the gastric wall (Fig. 1B). The tumor seemed to have invaded the pancreas and a few enlarged lymph nodes could be seen. Chest x-ray and other examinations showed no distant metastasis. Due to gastric bleeding along with the family members and patient's strong desire for surgery, the patient accepted surgery as the first treatment option. Total gastrectomy with D2 lymph node dissection was performed. It was found that the tumor was located on the lesser curvature of the stomach, and there was no other internal organ metastasis except for invasion of the upper edge of the pancreas which was resectable.

Grossly, the tumor was hard in consistency with massive necrosis, ulcerated in the center and broke through serosa (Fig. 2). Histologic evaluation revealed multiple different sections contained a proliferation of malignant epithelioid and spindle cells

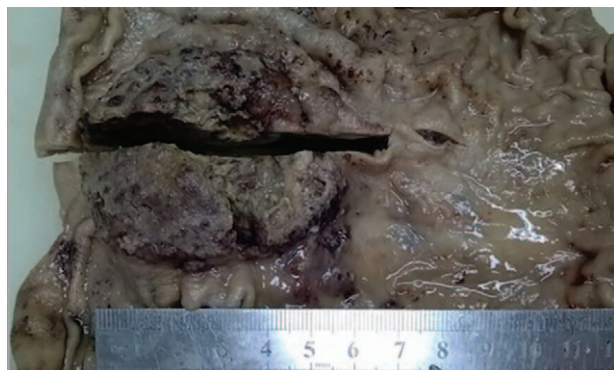


Figure 2. Gross appearance of the tumor: an irregular-surfaced tumor was hard in consistency and hemorrhagic, 7.0×5.5 cm in size.

arranged in sheets and slit-like/vascular spaces (Fig. 3). The lesion appeared to be centered in the deeper layers of the stomach (serosa and muscularis propria) with expansion up to the mucosa. Lesion cells, both in sheets and in slit-like vascular spaces showed moderate to marked nuclear pleomorphism and scattered mitoses. Extensive ulceration of the surface epithelium and hemorrhagic necrosis was seen. Spindle cells forming slit-like vascular spaces were also seen in the lymph nodes. Immunohistochemistry showed strong diffused expression of CK (AE1/AE3), CD31, ERG, FLI-1, EMA, CAM5.2, P53, CK7, and Vimentin (Fig. 4). The labeling index estimated at Ki-67 was 60%. In addition, a scattered positive was seen for P8. CD34 was patchily expressed in rare tumors. The tumor cells did not stain with EBER, HCG, c-Myc, P63, D2-40, c-erbB-2, PLAP, CD68, MelanA, HMB45, Desmin, SMA, DOG1, CD117, and S100. Furthermore, the lymph node cells also displayed strong and diffused CK (AE1/AE3), CAM5.2 and Vimentin. Other listed markers including CK20, CD45, and CDX2 were negative. These findings confirmed a diagnosis of angiosarcoma with epithelioid features in the stomach and metastatic angiosarcomas in the lymph nodes.

The patient recovered well after the surgery but unfortunately after about 1 month, he felt recurrent upper abdominal pain. So the patient came back and computed tomography (CT) and magnetic resonance imaging (MRI) examinations were performed again. The imaging suggested liver and retroperitoneal lymph node metastasis. Before the patient had any opportunity to undergo chemotherapy or other treatment, he died from multiple organ dysfunction syndrome (MODS) after about 2 months.

3. Discussion

Epithelioid angiosarcomas can arise from any location in the body, rarely occurring in stomach or other places in the abdomen. Gastrointestinal tract involvement is very rare and can be primary to the gastrointestinal tract or secondary to metastasis, whereas published papers on this rare subtypes are usually relating to liver, small intestine and spleen.^[3] With the improvement of diagnostic technology in recent years, reports about angiosarcomas in abdominal cavity have been increasing, which is often of the epithelioid type. Although the cause of epithelioid angiosarcomas is unclear, we also discovered some different risk factors like chronic lymphoedema, prior radiotherapy, exogenous toxins and chronic venous ulceration associated

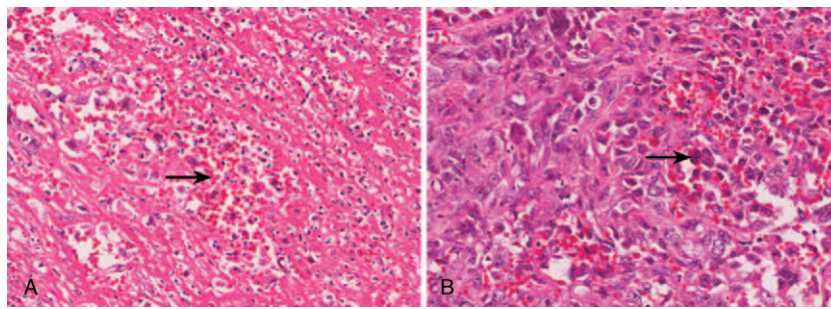


Figure 3. Histological appearance of the tumor: (A) Epithelioid and spindle cells lined slit-like/vascular spaces and single or small nests of cells grouped around a lumen containing red blood cells (arrow). (B) Epithelioid and spindle cells arranged in irregular channels (arrow) (hematoxylin and eosin stain; $\times 200$).

with epithelioid angiosarcomas.^[4] Especially the chronic venous ulceration may become an independent risk factor in the future research.^[5]

The mean age of patients with angiosarcomas reported in large cases was 65 years old, and 44% of them were women.^[6] Because of its nature of being highly aggressive and insidious growth, clinical symptoms of primary epithelioid angiosarcomas are not specific. Generally, either manifested bleeding, such as melena or hematochezia, or occult bleeding is a main symptom of gastrointestinal angiosarcomas. Melena has also emerged in the present case. Some cases are even asymptomatic, and accidentally discovered by routine gastroscopy examination. Unfortunately, these symptoms are associated with advanced disease, so early diagnosis plays an important role in the treatment of primary gastric epithelioid angiosarcomas.

We can use abdominal computed tomography and magnetic resonance imaging findings to detect the origin of tumors and its relationships with adjacent structures, but it is difficult to differentiate it from other tumors, including gastric stromal tumor or gastric adenocarcinoma. Abdominal computed tomography scans usually show irregular-margined mass with strong and persistent enhancement.^[7] Similar to other gastric tumors, direct visualization with an endoscopy and biopsy of the suspected lesions is an effective way to distinguish whether it is malignant or not.

Histologic and immunohistochemical studies are the gold standard to confirm the diagnosis. The histologic changes were summarized as follows: The tumors reveal slit-like/vascular spaces containing numerous erythrocytes, which are lined by atypical cells. And the atypical cells were large, spindle and,

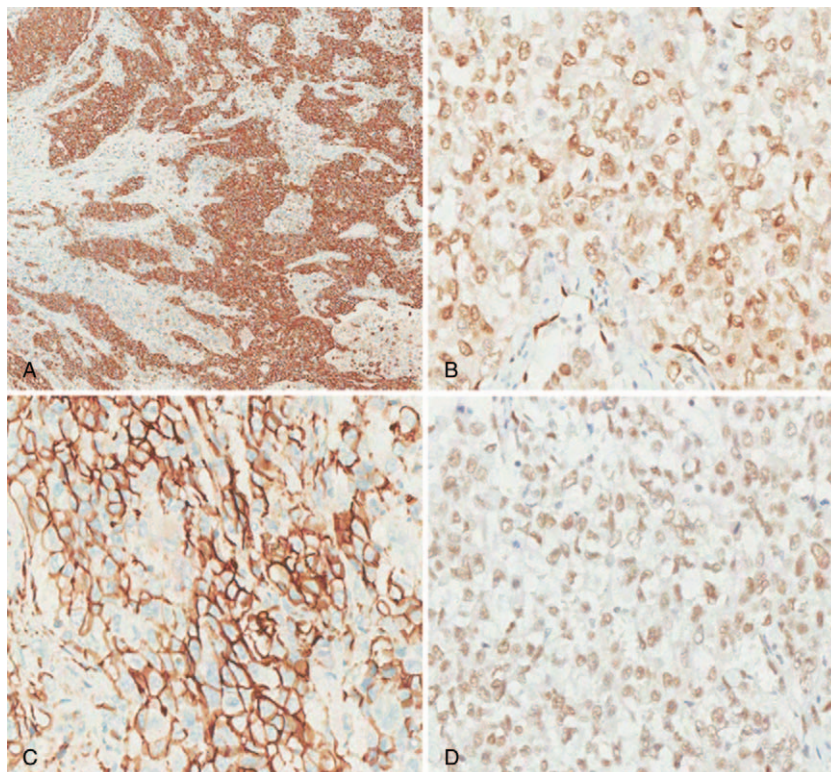


Figure 4. The tumor cells were positive for (A) CK (AE1/AE3); (B) ERG; (C) CD31; (D) FLI-1 ($\times 200$). CD=cluster of differentiation, CK=cytokeratin, ERG=ether-a-go-go-related gene, ETS=E-twenty-six, FLI-1=Freund leukemia integration 1.

occasionally, round to polygonal in shape.^[8] Endothelial cells are filled with abundant eosinophilic cytoplasm, and the nuclei with prominent nucleoli were plump, pleomorphic, and occasionally bizarre. Within the nucleus, the chromatin is peripherally marginated, yielding a vesicular appearance.^[9] Throughout the tumor, nuclear division and pathological mitotic figures can be seen. Meanwhile, numerous necrosis and hemorrhage are present.

Immunohistochemical study is the better way for us to make an accurate diagnosis of the epithelioid angiosarcomas. Factor VIII-related antigen and UEA-1 have been considered the most sensitive and reliable cell marker in the immunohistochemical evaluation of epithelioid cell derivation.^[9] Meanwhile, CD-31 antigen has been shown to be expressed by epithelioid cells, thereby adding another marker to the immunohistochemical armament for evaluating epithelioid cell derivation.^[10] Although this marker also stains histiocytes, megakaryocytes, and some other cell types,^[11] it is our experience that a strong and diffuse staining in a malignant solid neoplasm is fairly specific for endothelial origin. Recently, ETS (E-twenty-six) family transcription factors, including ERG and Freund leukemia integration site 1 (FLI-1), are both found to be consistently stained in vascular endothelial cells.^[12] In the absence of these stains, epithelioid angiosarcomas can easily be misdiagnosed as a carcinoma. In addition, cytokeratin (CK) expression has been documented in vascular tumors and is particularly common in epithelioid vascular neoplasms.^[13] Our case stained for a broad range of CK7 and CK (AE1/AE3). Moreover, epithelioid angiosarcomas are known to metastasize to lymph nodes which can also show CK (AE1/AE3). Additionally, CK20 have not been detected in present case.

Due to the rarity of randomized trials and prospective studies about primary gastric epithelioid angiosarcomas, treatment guidelines for this disease have not been defined. A 14-year retrospective review showed that overall 5-year survival rate for 125 patients with angiosarcomas at various sites, was 31%.^[14] However, patients with angiosarcomas of gastrointestinal organs usually die within 1 year after diagnosis.^[4] Surgery combined with adjuvant chemotherapy seem to be an alternative option for the treatment of epithelioid angiosarcomas.^[15] Paclitaxel-based chemotherapy was considered as the first choice. Complete surgical resection and negative microscopic margins can help patients gain a prolonged prognosis. Another recent phase II clinical trial for 27 patients showed that paclitaxel seemed to be effective in treating patients with unresectable angiosarcomas.^[16] The paclitaxel was given at a dose of 80 mg/m² on days 1, 8, and 15 for of a 4-week cycle, the median time to progression was 4 months and the median overall survival was 8 months. There was still a successful case reported that angiosarcomas could express PD-L1 and the patient had developed a good prognosis after received PD-L1 inhibitor pembrolizumab.^[17] Immunotherapy seems to be a great promising new treatment for angiosarcomas. The overall prognosis of epithelioid angiosarcomas remain poor, but there are still some significant adverse predictors of survival such as tumor size, tumor necrosis, metastases at presentation and the absence of surgical excision.^[18]

In conclusions, the poor prognosis and early metastases have revealed primary gastric epithelioid angiosarcomas are highly malignant and aggressive. For its insidious growth and relative rarity, diagnosis is often difficult and delayed, which can negatively affect survival. Histologic and immunohistochemical studies are the gold standard to confirm the diagnosis. Tumor makers of CD31, factor VIII, FLI-1, and ERG may be helpful for

the diagnosis of primary gastric epithelioid angiosarcomas. Surgery with chemotherapy seems to be the only potential approach for this disease.

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Author contributions

Conceptualization: Jie Xia, YiXiong Zheng, DiKe Shi, ZhiWei Wu, Yang Chen, BaoQing Liu, wongkamchai Metta, Li Chen.
Data curation: Jie Xia, YiXiong Zheng, DiKe Shi, ZhiWei Wu, Yang Chen, BaoQing Liu, wongkamchai Metta, Li Chen.
Formal analysis: Jie Xia, YiXiong Zheng, DiKe Shi, ZhiWei Wu, Yang Chen, BaoQing Liu, wongkamchai Metta, Li Chen.
Funding acquisition: Jie Xia, YiXiong Zheng, DiKe Shi, Yang Chen, BaoQing Liu, Li Chen.
Investigation: YiXiong Zheng.

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