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CASE REPORT

Primary Epithelioid Angiosarcoma of the Jejunal Mesentery Causing Abdominal Bleeding: Case Report and Literature Review

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Abstract: Gastrointestinal angiosarcoma is an extremely rare malignant tumor of the digestive tract, characterized by a very poor prognosis, with few patients surviving more than 1 year after diagnosis. This case report describes a 71-year-old female patient with a 3-year history of intermittent abdominal pain and significant exacerbation of abdominal pain and bloating 2 weeks prior to treatment. After surgical treatment, the pathological and immunohistochemical diagnosis was primary epithelioid angiosarcoma of the jejunal mesentery. The patient refused postoperative adjuvant chemotherapy and died 4 months after diagnosis due to widespread systemic metastasis. In addition, this article reviews 38 previously reported cases of primary gastrointestinal angiosarcoma, aiming to further understand angiosarcoma and thus guide clinical practitioners in providing more comprehensive treatment approaches.

Keywords: gastrointestinal, angiosarcoma, hematochezia

Introduction

Primary angiosarcoma is a rare malignant tumor originating from mesenchymal tissue, originating from endothelial cells and lymphatic vessels. Its etiology is still unknown, but increasing evidence suggests the presence of characteristic molecular changes, which may be related to complex mechanistic pathway dysregulation leading to vascular growth disorders.[1] Secondary angiosarcoma is associated with chronic lymphedema and exposure to radioactive substances.[2] Due to the ubiquitous presence of blood vessels and lymphatic vessels, angiosarcoma can occur in any part of the body and is often more common in the skin of the head and neck of elderly people. It presents as a protruding mass, resembling purple black papules. Due to its strong invasiveness and lack of effective treatment methods, the prognosis is poor.[3] Skin angiosarcoma is often treated with local expanded resection. Due to the strong invasiveness of the tumor, it is difficult to achieve curative resection or negative margins, which determines the prognosis of the disease. Most patients die within one year of diagnosis.[4]

Primary gastrointestinal angiosarcoma is even rarer, and most patients have a survival period of only a few months after diagnosis. Most of them die due to multiple organ failure caused by extensive metastasis of the tumor in the late stage.[5] More importantly, the clinical manifestations of gastrointestinal angiosarcoma are hidden and atypical, and patients often seek medical attention due to symptoms such as abdominal pain and black stools.[6] Most patients are already in the advanced stage when seeking medical attention, making treatment more challenging. Currently, there is no established treatment protocol for gastrointestinal angiosarcoma. In the majority of cases, surgery is the primary approach, followed by adjuvant chemotherapy postoperatively, with commonly used therapeutic drugs such as paclitaxel or doxorubicin.[7] Due to the fact that angiosarcoma originates from endothelial cells, targeted treatments such as anti vascular endothelial growth factor (VEGF) may benefit patients, but the therapeutic effect still needs to be confirmed by later clinical trials.[8,9]

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Primary angiosarcoma of the small intestine is extremely rare, with only a few dozen reported cases. Due to the lack of relevant understanding of this disease, this article presents a report. This case report presents a 71-year-old female patient with primary mesenteric angiosarcoma of the jejunum, accompanied by extensive abdominal, peritoneal, and diaphragmatic pleural metastases.

Case Report

The patient is a 71-year-old elderly woman who began to feel abdominal pain and discomfort 3 years ago. During this period, the abdominal pain gradually worsened and did not receive special treatment after rest. Two weeks ago, there was no obvious cause for significant abdominal pain and abdominal distension, making it difficult to tolerate. During the onset of the disease, the patient can self relieve without taking any medication. Abdominal pain is mainly in the middle and upper abdomen. In addition, when abdominal pain occurred nearly 2 weeks ago, it was accompanied by abdominal distension and relieved after exhaust. During the course of the disease, there was no history of bloody or black stools, no history of nausea and vomiting, no history of fever, and no significant weight loss recently. The patient has a history of hypertension for 7 years and has been regularly taking amlodipine besylate tablets since the onset of the disease, achieving satisfactory blood pressure control. The patient's occupation is a farmer, and detailed inquiries about whether there is a history of radiation or exposure to chemical toxins were denied. It is worth noting that the patient has a family history and their father died of esophageal cancer. Physical examination: There are no suspicious ecchymosis on the surface of the skin, the color of the lower eyelid is pale, the left upper abdomen is deeply tender and can touch a spherical mass about 10 * 6cm in size, and the bowel sound is weakened (once/minute). The whole blood cell count indicates a red blood cell count of 2.81 * 1012/L and hemoglobin of 85g/L, indicating a moderate anemia state. The results of coagulation related tests are all within the normal range. The results of tumor markers showed that carbohydrate antigen (125) 192.90U/mL (reference range<22.00 U/mL), ferritin 185.9ng/mL (reference range 5.0–130.0 ng/mL), and heat shock protein 90 α 351.25ng/mL (reference range 0.00~82.06 ng/mL). Abdominal computed tomography and enhanced imaging showed a 9.3 * 5.9cm abdominal mass, multiple metastases in the abdominal cavity, peritoneum, and diaphragmatic pleura, and fluid accumulation around the spleen, abdominal cavity, and pelvic cavity (Figure 1). Chest computed tomography showed no metastatic lesions. After discovering ascites, in order to determine the nature of the tumor through cytological examination, the patient underwent ultrasound-guided puncture and drainage of the ascites. Surprisingly, the drainage fluid was 500mL of deep red blood. Considering the continuous outflow of drainage fluid, a exploratory laparotomy was chosen for the patient. During the operation, deep red blood and clots were observed in the pelvic cavity, hepatic and renal crypts, and splenic and renal crypts. 300mL of deep red blood was aspirated under negative pressure. A dark red mass can be seen in the jejunum, approximately 90 cm away from the Treitz ligament. Multiple small nodules can be seen in the greater omentum and parietal peritoneum (Figure 2). Therefore, it was decided to undergo partial small intestine resection and side to side anastomosis of the small intestine, and to submit small intestinal masses and greater omentum nodules for pathological examination. The patient recovered well after surgery, and on the 11th day after surgery, the abdominal drainage tube was removed and discharged smoothly. Due to the patient's financial constraints, postoperative adjuvant chemotherapy was refused, and chemotherapy drugs were planned to use paclitaxel and thalidomide. After follow-up, the patient died of widespread systemic metastasis 4 months after diagnosis. Hematoxylin and

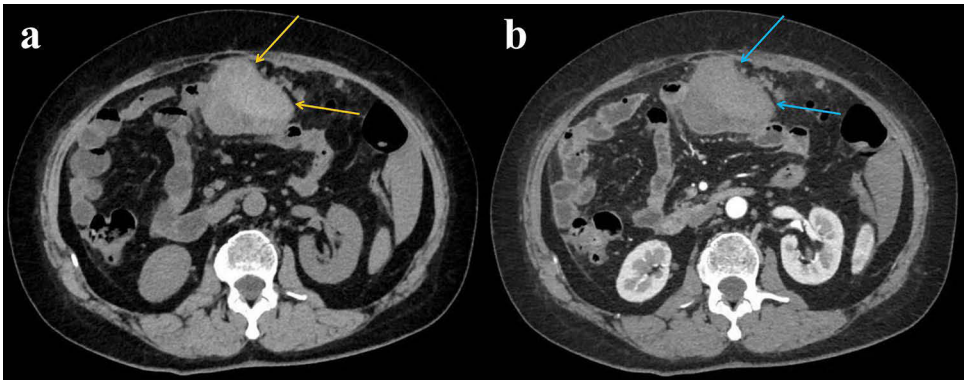

Figure 1 Abdominal computed tomography shows a slightly high-density heterogeneous mass of 9.3 * 5.9cm in the small intestine, with a density ranging from 34 to 57HU, indicated by yellow arrows (**a**). Enhanced scanning shows mild heterogeneous enhancement of the tumor, indicated by blue arrows (**b**).

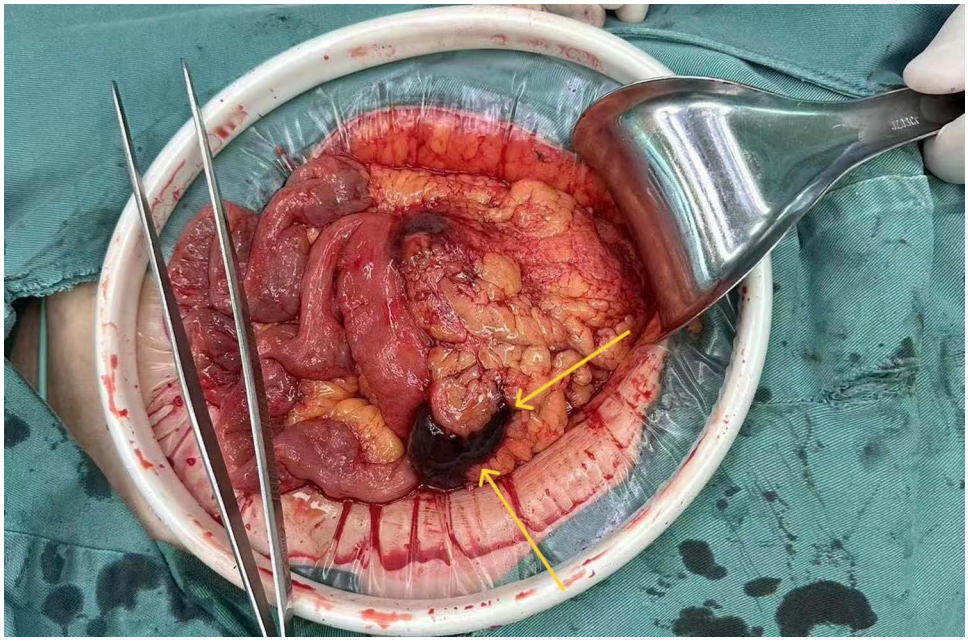

Figure 2 During the operation, a dark red mass was found on the left side of the upper abdomen, with some of the greater omentum adhering to it. It was approximately 90 cm away from the Treitz ligament and was approximately 10 * 6cm in size (yellow arrows).

eosin staining showed that the lesion was located in the mesentery of the jejunum, consisting of irregular vascular spaces. Some areas were anastomotic, with spindle shaped tumor cells and obvious atypia (Figure 3). Immunohistochemical staining showed that tumor cells expressed CD31, CD34, Fli-1, MDM2, ERG, and INI1 (Figure 4).

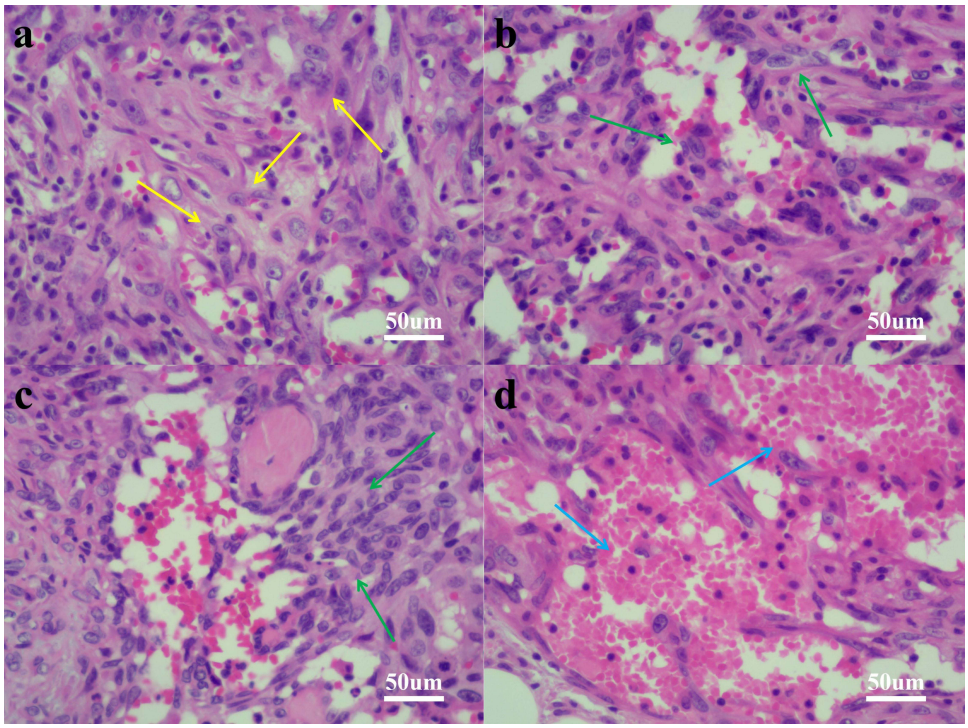

Figure 3 The lesion is located in the empty mesangium, with spindle shaped tumor cells and obvious atypia, indicated by yellow arrows (**a**). Tumor cells surround irregular blood vessel cavities, with green arrows (**b** and **c**). Some areas of the tumor show bleeding foci, indicated by blue arrows (**d**).

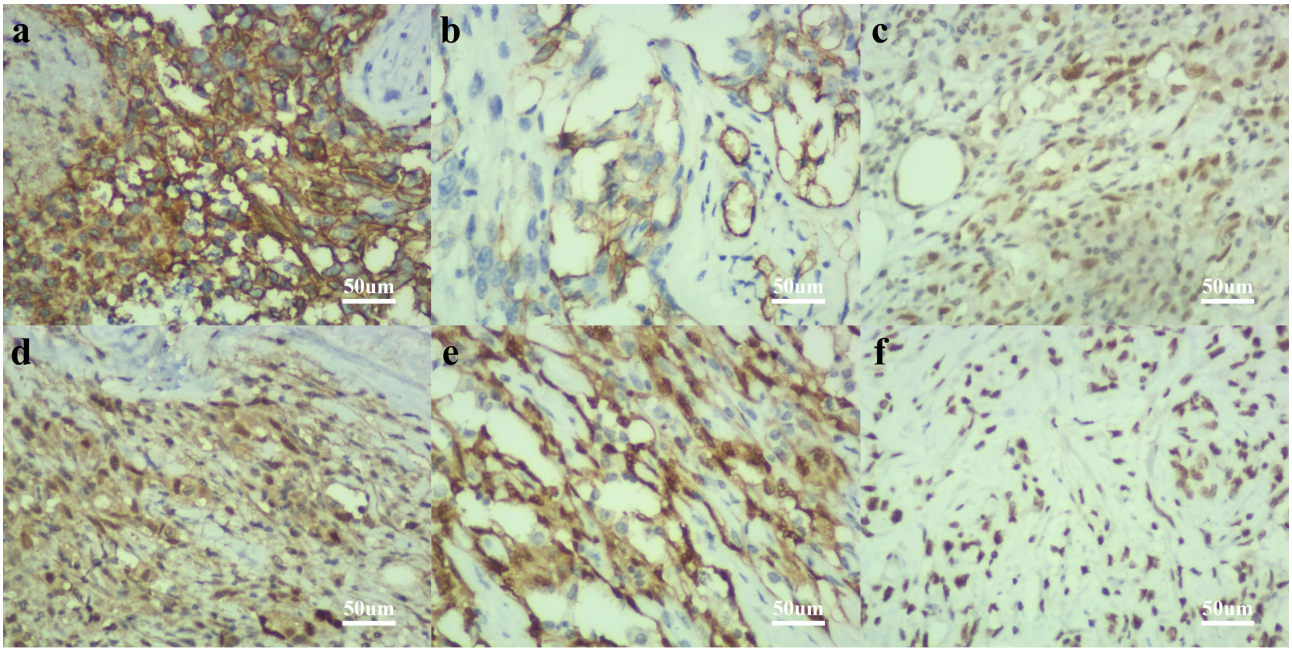

Figure 4 Immunohistochemical staining showed that tumor cells expressed CD31(**a**), CD34(**b**), Fli-1(**c**), MDM2(**d**), ERG(**e**), and INI1(**f**).

Discussion

Angiosarcoma originating from the small intestine is extremely rare in malignant tumors of the entire gastrointestinal tract, and its etiology is very unclear. However, it is worth noting that some patients have a history of radiation, and some of them develop gastrointestinal angiosarcoma lesions after radiation therapy due to previous malignant tumor diseases.[10] Another portion of patients are exposed to radiation environments for years due to occupational reasons, which can lead to illness.[11] In the current reports on cases of gastrointestinal angiosarcoma, the vast majority of patients have atypical clinical manifestations, mostly caused by late stage tumor necrosis and bleeding. Therefore, most patients have a history of abdominal pain and black stools, and are already in a moderate anemia state at the time of treatment.[12] Due to the atypical symptoms of gastrointestinal angiosarcoma and the lack of sensitive tumor markers, the possibility of angiosarcoma should be considered when highly suspected to be malignant. Therefore, it is important to pay attention to the differential diagnosis of gastrointestinal angiosarcoma, detect and intervene early, and improve the survival time of patients with angiosarcoma.

Due to the insidious onset of gastrointestinal angiosarcoma, patients often become in an advanced stage and metastasize to a distant location when not detected in a timely manner. Despite active surgical treatment and postoperative adjuvant chemotherapy, the majority of patients still have poor prognosis due to widespread metastasis and high invasiveness in the late stage of the tumor.[13] Unfortunately, the existing data lacks evidence-based medicine for gastrointestinal angiosarcoma, making the treatment of small intestinal angiosarcoma difficult. However, surgical resection remains the preferred option.[14] Currently, among the reported cases in the literature, chemical drugs such as paclitaxel, doxorubicin, thalidomide, vincristine, and cyclophosphamide are used for postoperative adjuvant chemotherapy.[10,15–17] However, these regimens are experimental and there is no clinical evidence to suggest their effectiveness. And these chemotherapy drugs are based on treatment plans for skin and other angiosarcoma, and their effects on gastrointestinal angiosarcoma are not ideal.[18]

Importantly, angiosarcoma originates from endothelial cells, and targeted anti VEGF therapy can be an important means of postoperative adjuvant therapy.[19] Therefore, gastrointestinal angiosarcoma may have a positive effect on targeted therapy, which is encouraging. Single anti VEGF therapy makes angiosarcoma cells susceptible to drug resistance. The combination of anti VEGF and programmed death 1 (PD-1) inhibitors

has shown positive effects in the treatment of angiosarcoma, but the effect is limited and cannot prevent tumor progression.[20] Angiosarcoma can occur in various organs of the body, and the tumor microenvironment and tumor cell metabolism exhibit significant heterogeneity, which may be the reason for the development of drug resistance in targeted therapy.[21] It is worth noting that pazopanib is a multi-target combination inhibitor that performs well in the treatment of skin angiosarcoma, with half of the patients having their tumors under control and a few patients even experiencing tumor shrinkage.[22] Therefore, combination targeted therapy should be an important adjuvant therapy for postoperative gastrointestinal angiosarcoma, and the selection of targeted drugs and their efficacy need to be further validated. Targeted therapy has brought new hope to patients with gastrointestinal angiosarcoma.

This article reviews previous reports on cases of primary gastrointestinal angiosarcoma, including a total of 38 patients with primary gastrointestinal angiosarcoma (Tables 1 and 2). The patient's age ranges from 11 to 86 years old, with a median age of 68 years.[17,23] Male patients are more than female patients, approximately three times as many as female patients. The occurrence of tumors does not seem to be significantly correlated with age. 27 patients had angiosarcoma originating from the small intestine, 9 from the colon, 1 from the rectum, and 1 from the stomach. Among them, 6 patients had a clear radiation history, 4 patients received multiple radiation treatments, 1 patient underwent multiple medical radiation examinations, and 1 patient was exposed to radiation due to occupational reasons. The vast majority of patients seek medical attention due to primary symptoms such as abdominal pain and black stools. Tumors were discovered through abdominal computed tomography, endoscopy, and other methods, and surgical treatment was performed. The vast majority of patients seek medical attention due to primary symptoms such as abdominal pain and black stools, and preoperative and intraoperative examinations are often mistaken for small intestinal stromal tumors. Therefore, the misdiagnosis rate of gastrointestinal angiosarcoma is extremely high, and diagnosis depends on pathological diagnosis. 7 patients underwent chemotherapy after surgery, but did not significantly change their survival time. Among them, 3 patients did not receive surgical treatment and had poor clinical prognosis. Nearly half of the patients had already experienced distant metastasis when the tumor was discovered, but there was no significant difference in clinical prognosis compared to patients who did not experience metastasis. It is worth noting that 3 patients who did not experience distant metastasis survived for more than 1 year after diagnosis. 1 patient survived for 4 years, but unfortunately ultimately died of acute myocardial infarction. According to pathological immunohistochemistry, gastrointestinal angiosarcoma highly expresses CD31, CD34, vimentin, and factor VIII. In addition, no sensitive tumor markers have been found for gastrointestinal angiosarcoma, and only 1 patient had a carbohydrate antigen 125 that was 4 times higher than normal.[24]

Most gastrointestinal angiosarcoma originate from the mesenchymal tissue of the gastrointestinal wall, while angiosarcoma originating from the mesentery are even rarer. The tumor in this case originated from the mesenteric blood vessels of the small intestine, and currently only one case has been reported. A 68-year-old patient with rectal mesenteric angiosarcoma presented with lower gastrointestinal bleeding due to the invasion of the tumor from the mesentery to the rectal mucosa, resulting in the tumor communicating with the intestinal cavity.[27] In this case, the tumor did not invade the intestinal cavity, but instead formed hidden bleeding in the abdominal cavity. The patient only presented with abdominal pain and anemia, making diagnosis more difficult. In addition, in the current reports of gastrointestinal angiosarcoma cases, the majority of tumors are multifocal, with very few being single isolated lesions.[48] On the one hand, the tumor has already undergone widespread metastasis at the time of discovery, and on the other hand, it may have its own invasive characteristics, making it easier to colonize through the bloodstream at a distant location. In summary, there is a lack of corresponding treatment guidelines for gastrointestinal angiosarcoma. Improving the prognosis of gastrointestinal angiosarcoma is a great challenge for clinical workers.

Table 1 A Retrospective Study Was Conducted on 38 Patients with Primary Gastrointestinal Angiosarcoma

Authors	Sex/Age (Years)	Radiation History	Symptoms	Site	Metastasis	Tumor Markers	Immunohistochemical	Treatment	Survival Time
Ni et al[5]	M/33	Not available	Abdominal pain, feeble, fever and weight loss	Small intestine	Liver and mesentery	None	Positive for CD31 and vimentin	Resection	Death 1 month after diagnosis
Tamura et al[15]	M/51	Not available	Hematochezia and weight loss	Small intestine	Bone	Not available	Positive for CD31, ERG, AE1/AE3 and CAM5.2	Resection, paclitaxel and adriamycin	Death 7 months after diagnosis
Policarpio et al[25]	F/51	History of cervical cancer radiotherapy	Abdominal distension	Small intestine	Mesentery	None	Positive for CD31, CD34 and factor VIII	Resection	Death 10 months after diagnosis
Mohammed et al[6]	F/25	Not available	Abdominal pain and weight loss	Small intestine	Colon	Not available	Positive for CD31	Resection	Death 3 months after diagnosis
Yu et al[8]	M/75	Not available	Hematochezia and feeble	Stomach	Small intestine	None	Positive for CD7, CD31, CD34, ERG, vimentin and P53	Resection	Death 1 month after diagnosis
Nai et al[10]	M/73	None	Black stool and feeble	Small intestine	None	Not available	Positive for CD34, vimentin, wilm's tumor-1 and vWF	Resection	Death 1 month after diagnosis
Liu et al[14]	F/43	None	Abdominal pain, feeble and weight loss	Small intestine	Peritoneum	None	Positive for CD31 and CD34	Resection	Death 3 months after diagnosis
Kolli et al[26]	M/76	Not available	Abdominal pain, feeble and weight loss	Small intestine	Mesentery	Not available	Positive for CD31, vimentin and ERG	Resection and paclitaxel	Not available
Zacarias et al[12]	M/84	Not available	Gastrointestinal bleeding	Small intestine	None	Not available	Positive for CD34, vimentin and factor VIII	Resection	Not available
Kamocki et al[27]	M/68	Not available	Gastrointestinal bleeding	Rectum	None	Not available	Positive for CD31	Resection	Still alive 4 years after diagnosis
Takahashi et al[28]	F/85	None	Abdominal distension and fever	Small intestine	Lung and mesentery	None	Positive for CD31, vimentin and factor VIII	Resection	Death 2 months after diagnosis
Abdulfattach et al[29]	M/77	None	None	Small intestine	None	Not available	Positive for CD31 and ERG	Resection	Not available

Louie et al[30]	M/78	Not available	Cachexia	Colon	Liver and Bone	Not available	Positive for CD31 and ERG	None	Death 1 month after diagnosis
Fraiman et al[11]	M/85	Not available	Abdominal pain and weight loss	Small intestine	None	Not available	Positive for CD31, CD34, vimentin and factor VIII	Resection and thalidomide	Still alive 1 year after diagnosis after diagnosis
Khalil et al[31]	M/68	Thirty years of radiation history	Abdominal pain and black stool	Small intestine	None	Not available	Positive for CD31 and CD34	Resection	Death 3 months after diagnosis
Huntington et al[32]	M/69	Not available	Black stool and feeble	Small intestine	Lung	Not available	Positive for CD31, ERG, AE1/AE3, MNF116, vimentin and factor VIII	Resection	Not available
Delvaux et al[33]	M/67	Not available	Abdominal pain	Small intestine	None	None	Positive for CD31	Resection	Death 3 months after diagnosis
Brown et al[13]	M/77	Not available	Hematochezia and weight loss	Colon	None	Not available	Positive for CD31, CD34 and factor VIII	Resection	Death 6 months after diagnosis
Lu et al[34]	M/67	Not available	Abdominal pain and black stool	Small intestine	Rectum and bone	Not available	Positive for CD7, CD31, CD34, ERG and INI-1	Radiotherapy and chemotherapy	Not available
Wu et al[24]	F/78	None	Hematochezia and feeble black stool	Small intestine	None	Not available	Positive for CD31, CD34 and ERG	Resection	Not available

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Table 2 A Retrospective Study Was Conducted on 38 Patients with Primary Gastrointestinal Angiosarcoma

Authors	Sex/Age (Years)	Radiation History	Symptoms	Site	Metastasis	Tumor Markers	Immunohistochemical	Treatment	Survival Time
Grewal et al[35]	M/73	History of radiation therapy for tonsil cancer	Black stool and feeble	Small intestine	Pharyngeal and mesentery	Not available	Positive for CD31 and CD34	Resection	Death 4 months after diagnosis
Ma et al[36]	M/70	None	Abdominal pain, black stool and feeble	Small intestine	Adrenal gland	None	Positive for CD31, CD34, vimentin, ERG and P53	Resection	Death 4 months after diagnosis
Navarro et al[18]	M/45	History of pelvic tumor radiotherapy	Abdominal pain, black stool and weight loss	Small intestine	None	Ca125 is 4 times higher than normal	Positive for CD31, AE1/AE3 and factor VIII	Resection	Not available
Watanabe et al[37]	M/70	Not available	Hematochezia	Colon	None	Not available	Positive for UEA-I, JC70, AE1, NCL5D3 and vimentin	Resection	Still alive 2 years after diagnosis
Watanabe et al[37]	M/64	Not available	Hematochezia	Small intestine	None	Not available	Positive for vimentin	Resection	Death 1 year after diagnosis
Lim et al[38]	F/44	Not available	Abdominal pain	Colon	None	None	Positive for CD31 and ERG	Resection and paclitaxel	Death 8 months after diagnosis
Hori et al[39]	F/20	Medical examination radiation history	Abdominal pain and hematochezia	Small intestine	Lung	None	Positive for CD31, CD141, ERG, CAM 5.2 and fli-1	Resection, carboplatin and paclitaxel	Still alive 2 years after diagnosis
Hui et al[40]	M/57	Not available	Hematochezia	Colon	None	Not available	Positive for CD31, CD34, fli-1, factor VIII, VEGR, EMA and ERG	Resection	Still alive 10 months after diagnosis
Tojo et al[23]	F/86	Not available	Oral swelling and feeble	Colon	Oral mucosa	Not available	Positive for CD31 and ERG	None	Death 2 months after diagnosis
Sadhu et al[41]	M/63	Not available	Hematochezia	Small intestine	None	Not available	Positive for CD31, PAX8, vimentin, fli-1 and ERG	Resection	Not available

Butrón et al[42]	M/59	Not available	Abdominal pain and hematochezia fever	Small intestine	Leg soft tissue	Not available	Positive for CD31, CD34 and fli-1	Resection, adriamycin and cyclophosphamide	Still alive 3 months after diagnosis
Ryu et al[16]	M/54	Not available	Abdominal pain and black stool	Small intestine	None	Not available	Positive for CD34, vimentin and factor VIII	Resection, ifosfamide and dacarbazine	Death 5 months after diagnosis
Zhang et al[43]	M/52	Not available	Abdominal pain and black stool	Small intestine	None	Not available	Positive for CD31 and CD34	Resection	Death 1 month after diagnosis
Kasper et al[44]	M/80	Not available	Leg pain	Colon	Bone	Not available	Not available	Resection	Death 9 months after diagnosis
Radić et al[45]	M/61	Not available	Abdominal pain, hematochezia and fever	Colon	Lumbar muscle	None	Positive for CD31, CD34, CD117, ERG and vimentin	Resection	Death 2 months after diagnosis
Castro et al[17]	F/11	Not available	Abdominal pain and weight loss	Small intestine	None	None	Positive for CD31	Resection, vincristine and adriamycin	Death 5 months after diagnosis
Hansen et al[46]	F/80	History of cervical cancer radiotherapy	Abdominal distension	Colon	Liver and small intestine	Not available	Positive for factor VIII	Resection	Death 1 month after diagnosis
Chahbouni et al[47]	M/25	Not available	Abdominal pain and weight loss	Small intestine	Mesentery	Not available	Positive for CD31, CD117 and factor VIII	Radiotherapy and adriamycin	Death 9 months after diagnosis

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Conclusion

Angiosarcoma is extremely rare in the gastrointestinal tract, and the tumor spreads rapidly, forming multiple metastatic lesions in a short period of time, resulting in poor clinical prognosis. Surgery is still the preferred treatment option, but surgery can only remove a portion of the lesion and is still powerless to prevent tumor spread. Therefore, postoperative drug assisted therapy is particularly important. Unfortunately, the chemotherapy regimen for skin angiosarcoma is not ideal in the treatment of gastrointestinal angiosarcoma. The combination of anti VEGF and PD-1 inhibitors in targeted therapy exhibits positive anti angiosarcoma activity, which is exciting. How to develop a reasonable treatment plan to get rid of the current predicament is an urgent problem that needs to be solved.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of The China-Japan Union Hospital of Jilin University. Written informed consent was obtained from the participants for publication of the details of their medical case and any accompanying images.

Consent for Publication

All authors and patients agree to publish.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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