World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v18.i44.6494

World J Gastroenterol 2012 November 28; 18(44): 6494-6500
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

CASE REPORT

Small intestine bleeding due to multifocal angiosarcoma

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Received: June 23, 2012 Revised: August 17, 2012
Accepted: August 26, 2012
Published online: November 28, 2012

Abstract

We report a case of an 84-year-old male patient with primary small intestinal angiosarcoma. The patient initially presented with anemia and melena. Consecutive endoscopy revealed no signs of upper or lower active gastrointestinal bleeding. The patient had been diagnosed 3 years previously with an aortic dilation, which was treated with a stent. Computed tomography suggested an aorto-intestinal fistula as the cause of the intestinal bleeding, leading to operative stent explantation and aortic replacement. However, an aorto-intestinal fistula was not found, and the intestinal bleeding did not arrest postoperatively. The constant need for blood transfusions made an exploratory laparotomy imperative, which showed multiple bleeding sites, predominately in the jejunal wall. A distal loop jejunostomy was conducted to contain the small intestinal bleeding and a segmental resection for histological evaluation was performed. The histological analysis revealed a less-differentiated tumor with characteristic CD31, cytokeratin, and vimentin expression, which led to the diagnosis of small intestinal angiosarcoma. Consequently, the infiltrated part of the jejunum was successfully resected in a subsequent operation, and adjuvant chemotherapy with paclitaxel was planned. Angiosarcoma of the small intestine is an extremely rare malignant neoplasm that presents with bleeding and high mortality. Early diagnosis and treatment are essential to improve outcome. A small intestinal angiosarcoma is a challenging diagnosis to make because of its rarity, nonspecific symptoms of altered intestinal function, nonspecific abdominal pain, severe melena, and acute abdominal signs. Therefore, a quick clinical and histological diagnosis and decisive measures including surgery and adjuvant chemotherapy should be the aim.

Key words: Gastrointestinal bleeding; Small intestine; Angiosarcoma; Small intestinal neoplasm

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Zacarias Föhrding L, Macher A, Braunstein S, Knoefel WT, Topp SA. Small intestine bleeding due to multifocal angiosarcoma. *World J Gastroenterol* 2012; 18(44): 6494-6500 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i44/6494.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i44.6494

INTRODUCTION

Primary malignant tumors of the small intestine are rare neoplasms, which comprise < 2% of all gastrointestinal tumors[1], including adenocarcinoma, carcinoid, sarcoma, gastrointestinal stromal tumors, and lymphoma. The reason for the poor prognosis of small bowel malignant tumors is partly due to a late diagnosis. The difficulty diagnosing this type of tumor is associated with the nonspecific symptoms, including nausea, vomiting, abdominal pain, constipation, generalized weakness, fatigue,

malaise, weight loss, anemia, diarrhea, ileus, intestinal perforation, or hemorrhage[2], as well as limited diagnostic methods for the small intestine.

Angiosarcoma is a rare mesenchymal tumor that most often arises from skin and subcutaneous tissues[3-7] but can ultimately arise anywhere in the body. Angiosarcomas have been described in the liver[8-11], spleen[12,13], adrenal glands[14-16], ovaries[17-19], heart[20-22], lung[23,24], breast[25-27] and, very rarely, in the gastrointestinal tract[28-32]. Consequently, an intestinal angiosarcoma that is located in the small bowel rather than the upper or lower gastrointestinal tract is a very rare medical condition. Angiosarcomas are aggressive tumors with a high rate of lymph node and peripheral metastases. This tumor arises as a *de novo* primary tumor or secondary to irradiation or chemical exposure. Angiosarcoma of the small intestine presents unique diagnostic challenges and is often discovered late, leading to a very poor prognosis.

Additionally, the histological diagnosis is difficult and can be confused with other neoplasms such as poorly differentiated carcinoma[4,33,34]. Diagnosis is facilitated by immunohistochemical expression analysis of the endothelial markers CD31 and CD34, as well as factor Ⅷ-associated antigens.

Herein, we describe the case of an 84-year-old man with the first episode of gastrointestinal bleeding due to angiosarcoma of the small intestine.

CASE REPORT

The patient was transferred to the Department of Internal Medicine of a peripheral hospital with gastrointestinal bleeding, which required a blood transfusion. Three lesions with coagulum and vessels necessitating application of two clips were found by endoscopy of the distal duodenum and upper segment of the jejunum. A colonoscopy revealed old blood, so bleeding in the small intestine was suspected. The patient had been diagnosed with an aortic aneurysm 3 years previously, which was treated with juxtarenal stent-graft prosthesis. A prosthetic-enteric fistula was suspected on the emergency abdominal aortic computed tomography (CT) scan. With this suspected diagnosis, the patient was transferred to the University Hospital Düsseldorf, and emergency vascular surgery was performed. The stent-graft prosthesis was removed and desobliteration of the saccular aortic aneurysm and the renal arteries was implemented, followed by implantation of an aorto-biiliacal silver-graft prosthesis. However, a prosthetic-enteric fistula was not revealed intraoperatively. The gastrointestinal bleeding did not arrest postoperatively, and Forrest IIb bleeding in the proximal jejunum was endoscopically diagnosed and treated. The local bleeding was stopped with hemoclips.

An exploratory laparotomy was performed due to persistent gastrointestinal hemorrhage, which showed multiple intra-abdominal hemorrhagic lesions in the intestinal wall of the jejunum (Figure 1). Three segmental resections and a distal loop jejunostomy were performed for a histological evaluation but achieved only temporal arrest of bleeding, which again became visible postoperatively after a loop jejunostomy. As no transanal bleeding was observed, and the histological analysis suggested a malignant angiosarcoma, a small bowel resection proximal to the loop jejunostomy with an end-to-end duodenoileostomy was subsequently performed.

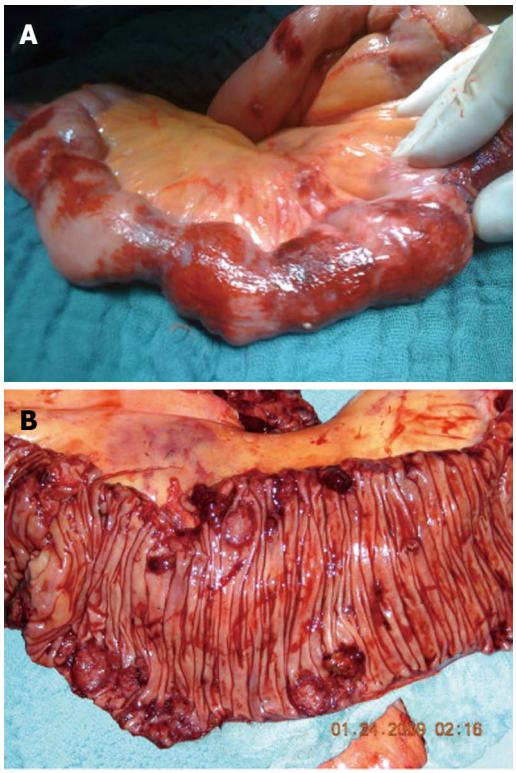

Figure 1 Multiple intra-abdominal hemorrhagic lesions in the intestinal wall of the jejunum. A: Intraoperative presentation of the jejunum with multiple subserous hemorrhages; B: Longitudinally lanced jejunum specimen with disseminated mucosal tumor manifestation.

Only approximately 1 m of small intestine could be preserved to achieve bleeding control. Adjuvant therapy was intended with paclitaxel, due to histological evidence of angiosarcoma. Unfortunately, a spontaneous intracranial hemorrhage with ventricular bleeding led to death of the patient, and the cause could not be determined. During hospitalization, the patient had received 75 erythrocyte concentrates, 49 units of fresh frozen plasma, 12 thrombocyte concentrates, and coagulation factors.

Histopathological findings

The small bowel showed an epithelium partly ulcerated with hemorrhage and infiltration of a mesenchymal fusiform tumor with parts of high-grade cells and nuclear polymorphism, including several mitoses and apoptosis formation (Figure 2). The tumor cells formed slit-shaped hollows, and they were predominantly grouped together with a solid appearance. The neoplastic cells were multifocal with macronucleoli. Eight mitoses were

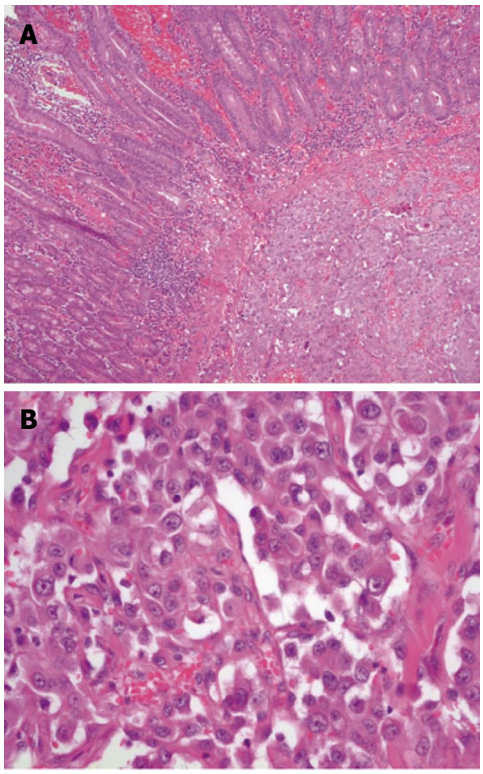

Figure 2 Histopathological findings. A: Ileum section stained with hematoxylin and eosin (HE) shows extensive tumor infiltration (× 100); B: HE-stained detailed section of an angiosarcoma with typical vascular proliferation (× 400).

identified per 10 high-power fields. The tumor cells stained positive for CD31, cytokeratin, and vimentin and slightly weaker for CD34. The tumor cells were also focally positive for factor Ⅷ. The MIB-1 marker of proliferation was expressed in approximately 40% of nuclei. The Berlin blue reaction indicated siderin deposits and Elastica-van-Gieson staining revealed collagen fibers. In summary, the tumor showed a less differentiated, multifocally growing epithelioid angiosarcoma (degree of malignancy Ⅲ Coindre) in the submucosa with infiltration of the subserosal fat tissue and extensive lymphatic spread.

DISCUSSION

A gastrointestinal hemorrhage is a potentially dangerous condition that warrants a quick diagnosis and decisive treatment. The vast majority of these bleeding events are due to either upper or lower gastrointestinal bleeding, and only 5% cannot be localized endoscopically[35]. These bleeding events typically occur from the small intestine. The most common cause of small intestinal bleeding is a vascular abnormality such as angioectasia, followed by tumors and, more infrequently, small bowel ulcers and aortoenteric fistulas[36]. Angiosarcoma of the small intestine is an extremely rare but potentially life-threatening cause of such bleeding.

Angiosarcomas typically occur in skin and superficial soft tissue, rather than in the gastrointestinal tract, and compromise < 2% of all sarcomas[37,38]. Consequently, only 33 cases of small intestinal angiosarcoma have been reported in the English literature over the past 42 years (Table 1).

The precise predisposing factors remain unknown. Exposure to vinyl chloride, thorotrast, arsene, and radiation have been associated with the pathogenesis[9,31,39-41]. Of the 33 cases reported, 14 describe patients developing an angiosarcoma after being treated with radiation for a malignant tumor, including ovarian carcinoma[39,42], ovarian dysgerminoma[40], squamous cell carcinoma of the uterine cervix[43-46], endometrial adenocarcinoma of the uterus[41,47], and Hodgkin's disease[48]. The first report of an angiosarcoma of the small intestine after postoperative irradiation was published in 1979[39]. That patient developed an angiosarcoma in the terminal ileum 8 years after irradiation for an ovarian carcinoma. Since then, 13 more angiosarcoma cases following radiation have been published (Table 1). In one case, an angiosarcoma occurred after exposure to irradiation and polyvinyl chloride[31], but predisposing factors could not be identified in the remaining 19 cases. The patient presented in this report also did not have any known malignancy or exposure to irradiation, vinyl chloride, or other chemicals known to induce angiosarcomas such as thorotrast or arsene.

Categorization by sex and age does not reveal any clear-cut distribution. The average age of patients with this type of angiosarcoma was 62 years (range, 25-87 years), and 18 patients were male and 15 were female (Table 1).

The clinical manifestations of patients with angiosarcomas of the small intestine include lethargy, weakness, altered intestinal function, nonspecific abdominal pain, severe melena, anemia, acute abdominal signs and/or ileus symptoms, and even nonspecific chest pain (Table 1). In 15 of the 33 cases, the patient had signs of gastrointestinal bleeding[30,31,37,49,50], similar to the patient described in this report. This variability in clinical manifestations makes it even more difficult to reach a quick and correct diagnosis. Furthermore, currently available diagnostic modalities, including CT, capsule endoscopy, double-balloon enteroscopy, magnetic resonance imaging, and positron emission tomography-CT all fail to detect the bleeding site, let alone lead to a diagnosis.

Angiosarcomas are classified as well-differentiated, poorly differentiated, and epithelioid tumors. A histological diagnosis can be challenging because angiosarcoma of the small intestine shows high architectural and cytological variability. The epithelioid morphology is typical but can be easily confused with other entities such as a poorly differentiated carcinoma[4,47]. Immunohistochemical expression analysis for the endothelial markers CD31, CD34, and factor Ⅷ-associated antigen is crucial. The majority of cases listed in Table 1 were positive for these antigens. Other antigens show limited relevance and can

Table 1 Literature overview: Angiosarcoma of the gastrointestinal tract (modified from Grewal *et al*[32] and Policarpio-Nicolas *et al*[47])

Patient [age (yr)/sex]	Tumor manifestation	Histology	Radiation/ pre-disposition	Symptoms	Therapy	Outcome	Ref.
46/M	Duodenum, ileum, and stomach	Epithelioid	None	Abdominal pain, melena	Resection	Died after 6 mo	[50]
65/F	Ileum	Well-differentiated	Radiation	Abdominal pain, nausea, vomiting	Resection, chemotherapy	Died after 14 mo	[39]
64/M	NA	Epithelioid	None	Gastrointestinal bleeding	Resection	Died after 1 yr	[29]
57/F	Small intestine	Epithelioid	None	NA	Resection	Died after 4 mo	[29]
47/F	Ileum	NA	Radiation	Abdominal pain	Resection, chemotherapy, radiation	NA	[40]
64/M	Small intestine	Well-differentiated tumor	None	Gastrointestinal bleeding	Resection	Died with disseminated disease after approximately 1 yr	[30]
57/M	Ileocecal valve, small bowel, and mesentery	Well-differentiated tumor	None	NA	Resection	Died after several days	[30]
76/M	Ileum	Mixed, well-differentiated and epithelioid	None	Abdominal pain, poor appetite, fatigue	Resection	Died after 9 d	[59]
74/F	Jejunum	Well-differentiated	NA	Melena	Resection	Died due to multiple complications	[60]
51/M	NA	Well-differentiated	Radiation	Abdominal pain	Resection, chemotherapy	Died after 5 mo	[48]
76/F	Ileum	Well-differentiated	Radiation	Abdominal pain, weight loss, vomiting, diarrhea	Resection	Died after 5 mo	[45]
48/F	Ileum	NA	Radiation	Abdominal pain	Resection	Died from sepsis after 23 d	[43]
60/F	Small intestine	Well-differentiated	Radiation	Acute abdomen, and a distal jejunal perforation	Resection	Died after 3 mo	[44]
80/F	Small and large bowel	Well-differentiated	Radiation	Altered intestinal function	Resection	Died after 2 wk	[42]
69/F	Small and large bowel	Well-differentiated	Radiation	Weight loss, abdominal distention, hematochezia	Resection	Died after 23 d	[42]
NA/M	Duodenum, stomach	Epithelioid	None	Severe melena	Resection	Died of respiratory failure, metastases were found in various organs, including the lungs, bones, liver, gall-bladder, and lymph nodes	[61]
78/F	Small intestine	High-grade	Radiation	Relative bowel obstruction	Resection	Died after 2 yr	[41]
50/F	Ileum	Multifocal and infiltrating	Radiation	Repeated symptoms of intestinal obstruction	Resection, chemotherapy	Died after 21 mo	[41]
61/F	Ileum	Well-differentiated	Radiation	Fullness, abdominal pain	Resection	Died after 10 mo	[46]
67/M	Jejunum, ileum	Epithelioid	None	Weight loss, Intermittent severe abdominal pain, and melena	Resection	Died after 3 mo	[51]
85/M	Small intestine	High-grade	None	Weight loss, decreased appetite, generalized weakness, left upper quadrant abdominal pain	Resection, chemotherapy	Survived at least 1 yr	[52]
59/M	Ileum	Mixed epithelioid and well-differentiated	None	Gastrointestinal bleeding	Resection	Died after 11 d	[37]
70/M	Duodenum	Epithelioid	None	Melena, anemia	Chemotherapy	Died after 4 mo	[49]
84/F	Jejunum	Epithelioid	None	Melena, anemia, shortness of breath	NA	Died after 17 mo	[49]
47/M	Jejunum	Epithelioid	None	Melena, anemia, shortness of breath	NA	Died after 4 mo	[49]
25/M	Small intestine	Epithelioid	None	Gastrointestinal bleeding, hemoptysis, anemia	Chemotherapy, radiation	Alive 18 mo after diagnosis, palliative situation	[49]

70/M	Ileum	Mixed, well-differentiated	None	Abdominal pain, vomiting	Resection, chemotherapy, radiation	Survived at least 4 yr	[53]
68/M	Ileocecal	High-grade	Radiation, polyvinyl chloride	Gastrointestinal bleeding, melena	Resection	Died before starting chemotherapy	[31]
51/F	Ileum	Well-differentiated	Radiation	Decreased appetite and vague abdominal pain of several months duration	Resection	Died after 10 mo	[47]
87/M	Duodenum, jejunum	Epithelioid	None	Lethargy, weakness, and nonspecific chest pain	Endoscopy, argon plasma coagulation	Died after 6 wk	[62]
73/M	Duodenum, jejunum	Epithelioid	Radiation	Weakness, dizziness, constipation, and melena	Resection	Died after 4 mo	[32]
NA/M	Jejunum	NA	NA	Acute abdominal signs	Resection, chemotherapy	Survived at least 3 yr	[2]
25/F	Small and large bowl	NA	None	Intermittent abdominal pain, weight loss, and progressive abdominal distension, a 7-wk history of shortness of breath, hematemesis, and melena	Resection	Died after 2 wk	[63]

NA: Not available; M: Male; F: Female.

cause confusion with other carcinomas. There is some controversy about the relevance of cytokeratin, which has been reported positive by some authors[32,37,49,51]. However, most authors have reported no such expression by intestinal angiosarcomas[29-31,48,52].

The current therapy for angiosarcoma includes bleeding control and symptomatic therapy to stabilize the patient, followed by radical tumor resection.

Six patients in the literature received adjuvant chemotherapy[39,41,48,49,52], and three patients were treated with combination chemotherapy and radiation[40,49,53]. Adjuvant therapy with paclitaxel was intended in the present case; however, the patient died before starting chemotherapy. All adjuvant therapy protocols are generally empiric and based on studies of cutaneous angiosarcoma, as randomized clinical studies on gastrointestinal angiosarcomas are lacking due to their rarity. The first case published received combination chemotherapy consisting of doxorubicin, vincristine, dacarbazine, and cyclophosphamide, after operative resection of the terminal ileum. That patient survived 14 mo[39]. Another combination therapy that has been used is doxorubicin and dacarbazine, which led to 5 mo survival after diagnosis[48]. Monotherapy with doxorubicin showed survival of 21 mo, at which time the tumor was widely disseminated[41]. Furthermore, thalidomide therapy was initiated as an experimental measure after operative resection in one case[52]. That patient was still alive 1 year after the initial diagnosis. No recommendation can usually be made, but paclitaxel and/or thalidomide are currently commonly considered[52,54,55]. The newest studies suggest administering doxorubicin and paclitaxel weekly for cutaneous angiosarcoma, which seem to provide longer progression-free survival[56-58].

Despite all efforts, survival of patients with small bowel angiosarcoma is generally poor. Survival usually ranges from several days after surgical intervention to 2 years. The majority of patients die within 6 mo to 1 year after being diagnosed (Table 1). Only two reported patients survived > 2 years after resection and adjuvant (radio-) chemotherapy[2,53].

One major cause of this poor outcome seems to be that the diagnosis is difficult, and many tumors are diagnosed only in the late stages of the disease. Therefore, a quick diagnosis using endoscopy and imaging procedures, as well as fast and decisive surgical intervention and adjuvant chemotherapy are necessary.

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