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Case Report

Primary post-radiation angiosarcoma of the small bowel. Report of a case and review of the literature

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Summary
Angiosarcomas developing in unusual sites such as the small bowel are rare, and fewer than 65 cases have been reported in the literature. They are not uncommonly associated with a known eliciting factor. Thus, among hitherto described cases of angiosarcoma of the small bowel, 16 were radiation-induced. One additional example of ileal post-irradiation angiosarcoma (PRA) in a 72-year-old female patient with a past history of uterine leiomyosarcoma is herein reported as a reminder of this causal association. The morphologic and immunohistochemical clues leading to the correct diagnosis of PRA of the small bowel and the differential diagnostic problems are discussed; a comprehensive review of the literature has also been performed with a focus on survival.

Key words: angiosarcoma, small bowel, radiation

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Introduction

Postradiation sarcomas are uncommon malignant mesenchymal tumors with most reported cases diagnosed as malignant fibrous histiocytoma and less often as fibrosarcoma or osteosarcoma. Criteria to attribute a malignancy to be radiation induced are history of radiation, long latent period, histologically proven malignancy within the field of irradiation, and different histology of the new tumor if radiation was given for malignancy [1]. It is estimated that 50% of all cancer patients receive radiotherapy and, in particular, radiation is a proven efficacious treatment for breast carcinoma [1].
Most of the documented cases of postradiation angiosarcoma (PRA) are occurred in breast skin and underlying soft tissues including the chest wall. The remainder of the cases of PRA have been documented in various locations, but rarely occur in the gastrointestinal tract.
In this paper, we describe a case of PRA of the small bowel. We discuss the clinicopathological features and differential diagnosis, according to the previous literature review.

Case report

A 72-year-old woman was referred to the Emergency Department of

Hospital "San Giovanni di Dio", Crotone (Italy) because of intermittent abdominal pain and recent symptoms of intestinal obstruction. Review of medical history yielded positive results for uterine leiomyosarcoma diagnosed 24 years before presentation. At that time, after total hysterectomy, she had received external beam radiation (irradiation dose unknown) to the lower pelvis. Colonoscopy performed in March 2017 was unremarkable. An abdominal plain film was obtained, which showed dilated intestinal loops with transitions to nondilated ones, and intestinal tympanites.

At laparotomy, there were small bowel loops adhering to the pelvic floor, as well as a mass in the ileum at about 20 cm from ileocecal valve with dilatation of the small intestine proximal to it. The adhesions were sectioned and the bowel mobilized. Additionally, small intestine resections were performed at three different consecutive sites, one of them due to the severe bowel stricture, and the others due to risk of dehiscence of the first side to side isoperistaltic anastomosis and setting up of a new side to side antiperistaltic definitive anastomosis.

On gross examination, the longer piece corresponded to a 36 cm-long segment of small intestine revealing a narrowed tan central zone, measuring 2 cm in largest diameter, with superficial erosion. Light microscopy, at low-power field, showed a diffuse infiltrative prevalently submucosal growth of epithelioid to spindle cells with subtle clefting suggestive of vascular differentiation. Sheets and strands of epithelioid elements focally filled the lamina propria preserving the overlying glands and causing mucosal ulceration (Fig. 1). High-power features of the lesional cells included a scant amount of eosinophilic cytoplasm and a round to spindle nucleus with coarse chromatin, a sometimes prominent nucleolus, and cellular necrosis (Fig. 2). There were occasional intracytoplasmic lumina that contained red blood cells (Fig. 3). The mitotic activity was high with up to 29/10 high-power fields. Immunohistochemical studies showed diffuse expression of CD31 and vimentin and negative staining for AE1/AE3 and Cam 5.2 keratins, CD34, desmin, α-smooth-muscle actin, chromogranin, CD56, PAX-8, HHV-8, S-100 protein and h-caldesmon confirming the diagnosis of PRA. Furthermore, the tumor had a MIB-1 index of 80% (Fig. 4). Surgical margins of the specimen were viable and free of infiltration.

The patient was referred to Oncology center to receive adjuvant therapy. She was discharged in good general conditions at 6 days after surgery, and the follow-up of 26 months remained uneventful.

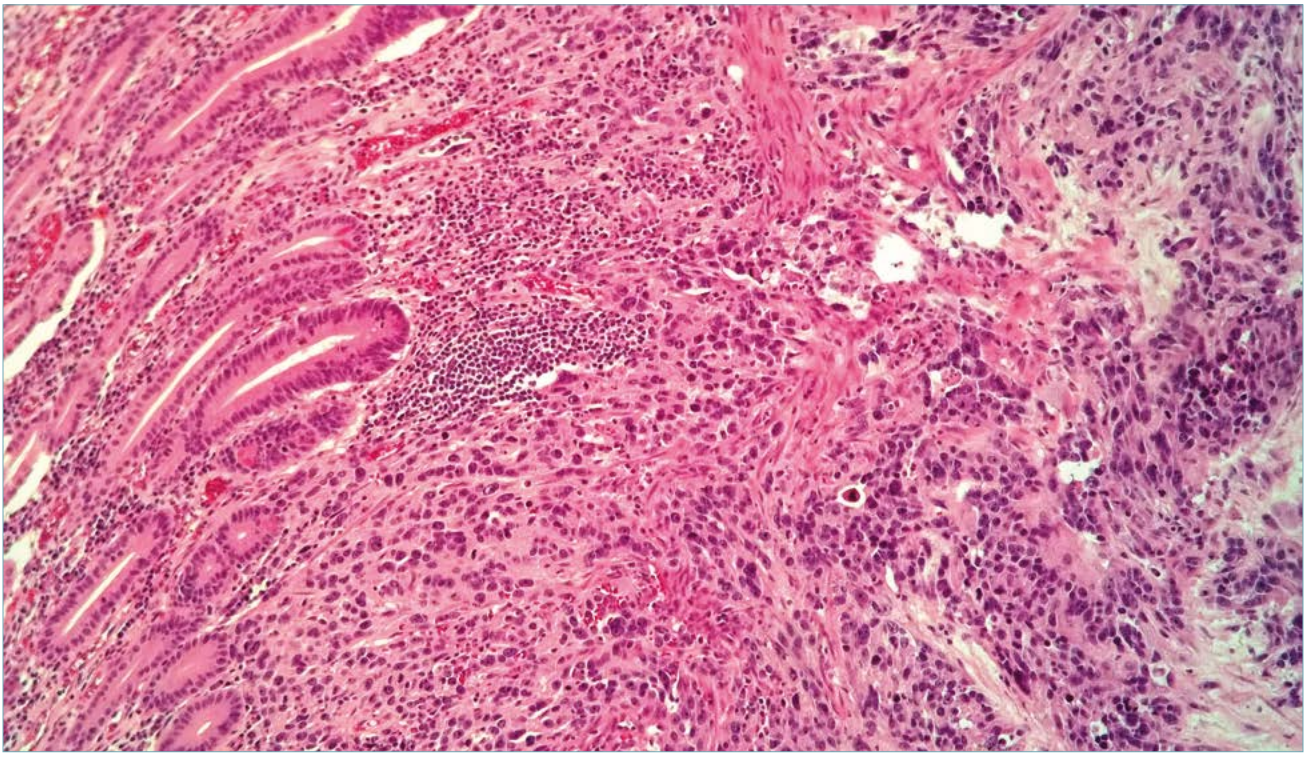

Figure 1. The tumor was located in the mucosa and submucosa layer and had a predominantly solid growth pattern.

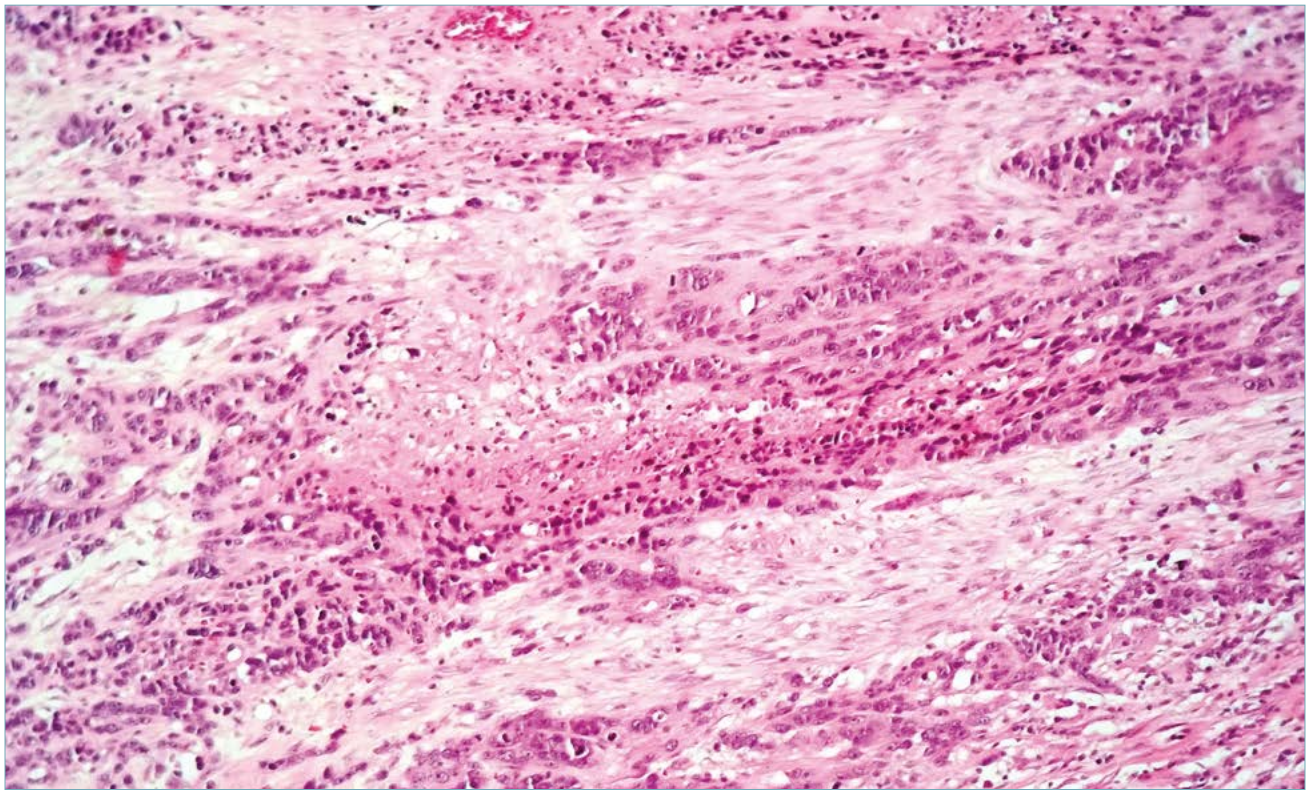

Figure 2. Sheets and cords of epithelioid to spindle neoplastic cells with eosinophilic cytoplasm and central necrotic zone.

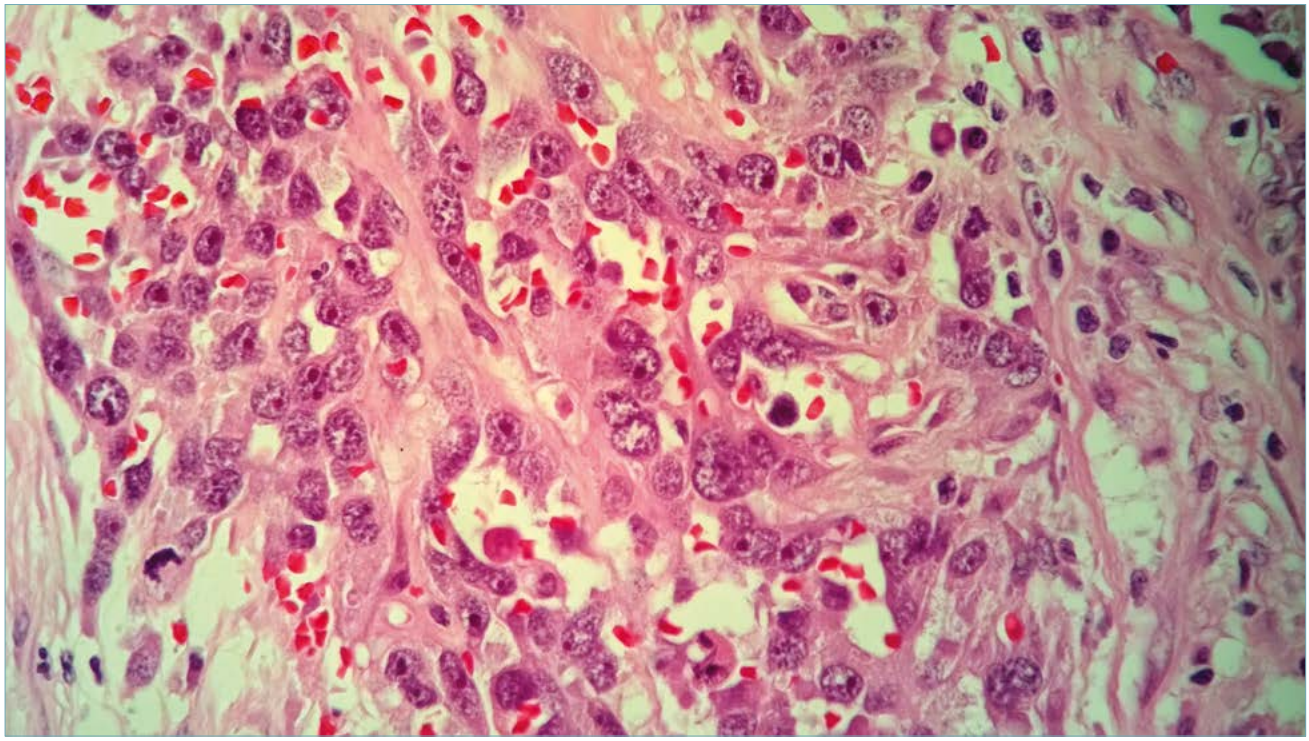

Figure 3. High-power view of the neoplasm displaying tumor cells with lightly eosinophilic cytoplasm, large vesicular nuclei and prominent nucleoli. There are subtle clefting and the presence of intracytoplasmic lumina containing red blood cells suggestive of vascular differentiation.

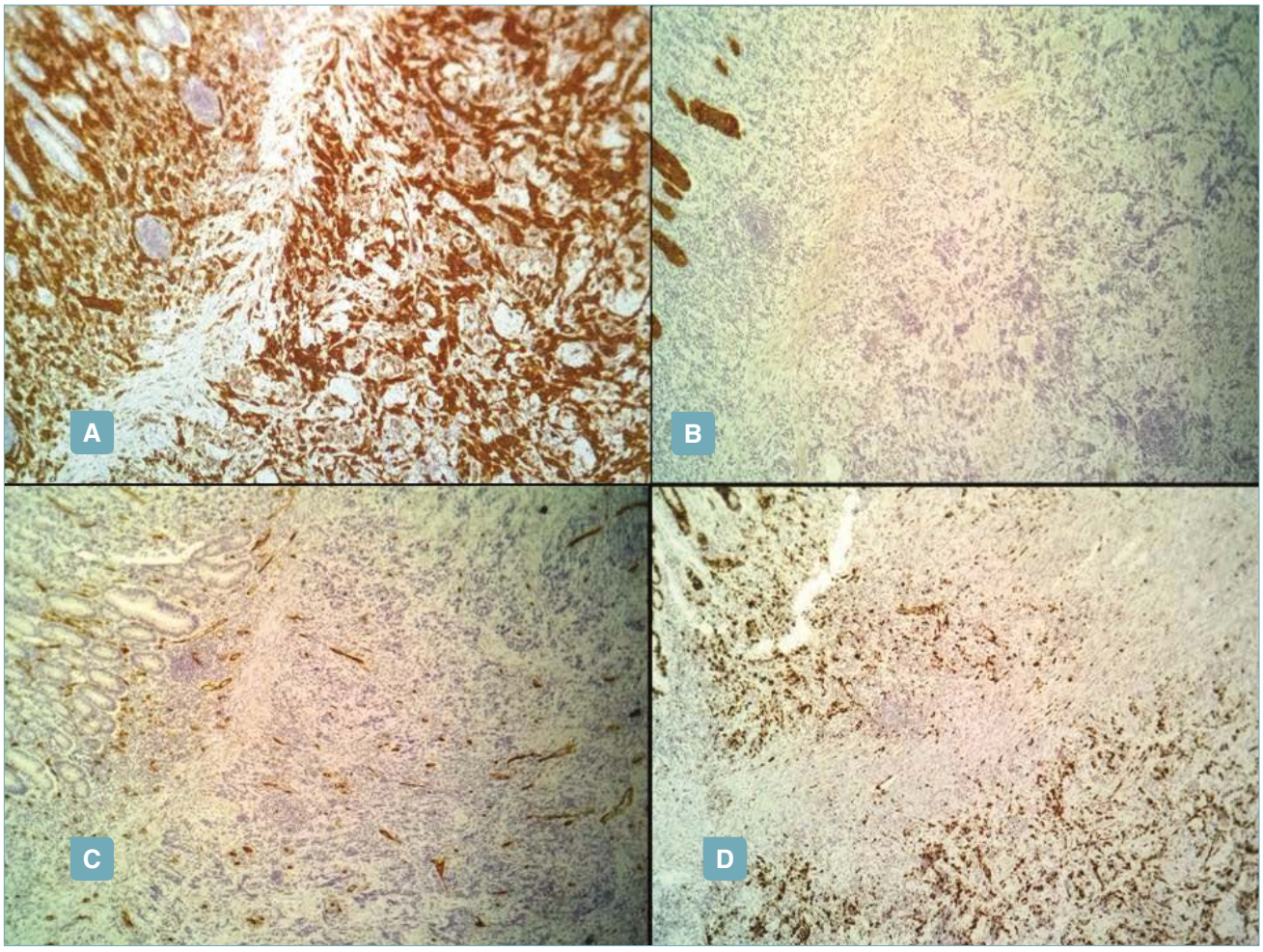

Figure 4. (A)The spindle to epithelioid tumor cells are strongly positive for CD31; (B) The neoplastic cells are negative for AE1/AE3 cytokeratin; (C) No staining of tumor cells for CD34; (D) High proliferative index of tumor cells with MIB1 immunostaining.

Discussion

Primary malignant tumors of the small bowel are unusual, comprisizing less than 2% of gastrointestinal tumors. Among these, the great majority are malignant carcinoids, adenocarcinomas and leiomyosarcomas, whereas other soft tissue tumors are very rare [2].
Angiosarcoma is a malignant tumor characterized by the hyperproliferation of cells with endothelial vascular features. These very rare neoplasms represent about 1-2% of all sarcomas and can occur anywhere in skin and subcutaneous tissues, particularly in the head and neck region. Angiosarcoma infrequently presents primarily with disease of internal organs, predominantly liver, spleen and adrenals [3].
In a review of 106 cases of gastrointestinal vascular tumors seen at the Mayo Clinic between 1925 and 1944, only 14 angiosarcomas were found, 3 of which in the small bowel [4]. Over the years, rare cases proposed to represent angiosarcoma have also been described in several reviews of primary malignancies of the small intestine, in scattered case reports and small series [5,6]. From 1949 to date, a Medline search using the key words “angiosarcoma” and “small bowel” revealed about 61 cases of primary angiosarcoma of the small bowel [1-52]. From published data, including the current case, the age of presentation ranged from 22 to 87 years (mean, 60.8 years) and there were 21 women (35.6%) and 38 males (64.4%), and two patients whose gender was not specified [1-52]. The male to female ratio was: 1,8:1. In our review of literature, the predominant presenting signs and symptoms for this rare entity were gastrointestinal bleeding, which occurred in 29 patients (49.1% of cases) and abdomi-

nal pain (44% of cases), often associated with anemia (28.8% of cases) [1-6,9,11-19,21-28,30-35,37-39,42,43,45-52]. In addition, these patients were often submitted to frequent blood transfusions, and death sometimes resulted from incontrollable hemorrhage. There were only eight cases that showed clinical evidence of small bowel obstruction [7,19,27,30,39]. Three patients had a history of initial perforation and acute abdomen, and the clinical picture of another case was thought to be consistent with an appendiceal abscess [5,22,31,36].

Because of the relative inaccessibility of the deep small bowel for endoscopic investigations and the lack of accuracy of radiographic features, the preoperative diagnosis of small bowel angiosarcoma remains unlikely. The conventional diagnostic methods, such as traditional endoscopy, barium studies, and even technetium 99m-labeled erythrocyte scan might leave the physician without an answer, and capsule endoscopy or MR enteroclysis might help detect the source of bleeding, only in some cases [3,14,18,21,27]. Briefly, in almost all patients reported in literature to date, including the current case, the correct diagnosis of angiosarcoma was made postoperatively after histologic and immunohistochemical examination of the surgical specimen. The association between angiosarcomas and certain environmental toxins or previous external-beam radiation therapy is well-documented. Occupational exposure to vinyl chloride, thorotrast and arsenic has been associated with its pathogenesis [2]. Furthermore, studies have clarified the relationship between angiosarcoma, chronic lymphedema of various etiologies and genetic factors, as neurofibromatosis NF-1, Klippel-Treunaney and Maffucci syndromes, mutated BRCA1 or BRCA2 [6,26]. To date, of the 61 reported cases, only 17 (27.8%) have been examples of PRA arising in the small bowel (including the case under discussion) [1,2,7,10,19,20,29,31,36-40,42]. Documented cases of PRA of the small bowel are listed in Table I. There was a significant difference in the incidence between male and female and most patients were women (male to female ratio:1:3). Patients were irradiated earlier for various cancers, including Hodgkin's lymphoma, chondrosarcoma, endometrial and cervical carcinoma, uterine leiomyosarcoma, and ovarian malignancies [1,7,10,19,20,29,31,36-40]. The rest of them were two male subjects, one with a history of antecedent radiotherapy for unknown pelvic tumor and the other with a prolonged exposure to both occupational radiation and polivinyl chloride [2,42]. Additionally, considering the long-term involvement of two patients in the construction industry, they might have also been exposed to chemicals implicated in the cause of this disease [23,49]. Apart from radiation and chemicals, angiosarcomas are also induced by foreign bodies [50]. Though there are many cases of foreign body associated sarcomas of various sites, it is rare in the intestinal tract possibly due to fewer chances of harboring foreign bodies at this site [2,50]. The interval between radiation and presentation of PRA ranged from 3 to 24 years (mean, 11 years) [1,7,10,19,20,29,31,36-40,42]. The terminal ileum was the most common location of PRA reported in the small bowel (at least 8 of the 17 cases) [1,7,20,31,36,37,40]. In two patients the neoplasm spread locally to involve the large bowel [39]. Approximately 45-50% of patients presented with advanced local disease due to multifocal intestinal involvement and early widespread metastasis to intra-abdominal and pelvic structures, including the peritoneal surface [2,7,10,20,29,31,42]. Patients who survived for longer periods developed intractable local disease and distant metastasis to liver, spleen, lungs and pleura [1,10,19,31,36,37,39,40]. Overall, 15/17 of patients had follow-up information available [1,2,7,10,19,29,31,36-40]. Follow-up ranged from 14 days to 36 months, mean = 11 months [1,2,7,10,19,29,31,36-40]. Of the 15 patients, all were died of disease at variable time points – from 14 days to 36 months – except two, one which was alive with disease at 21 months and the other, our patient, which had no signs of recurrence at 26 months. Prognostically, PRAs resemble other small bowel angiosarcomas (follow-up data: from 9 days to 48 months, mean = 10.4 months, average survival time of about 30 weeks) including poor response to combined chemotherapy regimens [4-6,8,9,11,12,15,17,18,23-26,28,32-34,41,43,44,46-49]. Therefore, the aggressive biologic behavior of PRA of small bowel is of no surprise.

Macroscopic findings of PRA of the small intestine frequently include a markedly hemorrhagic appearance with poorly defined thickening of the bowel wall and/or black nodules scattered on the serosal surface. Microscopically, our case was similar to the previously reported ones. The histopathologic evaluation of PRA, similarly to non-radiation-induced angiosarcoma arising in superficial soft tissue and gastrointestinal tract, can be a challenge, as it can exhibit histologic differentiation varying from benign appearing vascular proliferation to undifferentiated malignancy, with slit-like vascular channels and sheets of spindle to epithelioid neoplastic cells with or without intraluminal red blood cells, as the sole evidence of vascular differentiation. The presence of a lobular architecture and/or a papillary growth pattern, particularly when localized, are a histologic presentation that includes rare benign vascular proliferations occurring in the gastrointestinal tract related to intussusception and mucosal prolapse and the intravascular papillary endothelial hyperplasia. These lesions show minimal nuclear atypia and low mitotic rate [53].

Other differential diagnostic considerations include

Table I. Reported cases of PRA of the small bowel.

Reference	Sex/ age (years)	Presentation	Location	Metastasis	Follow-up	Radiated for	Radiation dose	Years after radiation
Chen et al. (37)	F/66	Abdominal pain, nausea, and vomiting	Terminal ileum	Liver	DOD at 14 months	Endometrioid adenocarcinoma / ovary	60 Gy	8
Nanus et al. (36)	F/42	Perforated distal ileum	Distal ileum	Labia majum, vagina, pelvis, urinary bladder, rectovaginal septum, paraortic LNs, lungs, abdomen	DOD at 36 months	Dysgerminoma/ ovary	48 Gy	16
Wolov et al. (39)	F/80	Peripheral edema, abdominal distension, altered bowel function, mucus per rectum	Small and large intestines	Peritoneum, liver	DOD at 2 weeks	Squamous cell carcinoma/uterine cervix	55Gy	20
Wolov et al. (39)	F/69	Anorexia, weight loss, abdominal distension, hematochezia	Small and large intestines	Pleura and peritoneum	DOD at 23th hospital day	Stage IB, grade 3 adenocarcinoma/ uterus	50Gy	7
Berry et al. (10)	M/51	Peritonitis	Small bowel	Pleura	DOD at 5 months	Stage IIA Hodgkin's lymphoma	Total nodal irradiation	3
Su et al. (40)	F/48	NA	Terminal ileum	Liver and local recurrence	DOD at 23thday	Squamous cell carcinoma/uterine cervix	NA	3,2
Hwang et al. (38)	F/60	Anorexia, abdominal pain, abdominal distension	Small intestine	NA	DOD at 2 months	Stage IIIB carcinoma/uterine cervix	96,50 Gy	8
Hansen et al. (19)	F/76	Watery diarrhea, vomiting, abdominal pain, weight loss	Small bowel	Serosal surface of stomach, small and large bowel, liver, spleen, urinary bladder	DOD at 5 months	Endometrial adenocarcinoma/ uterine corpus	45,1 Gy	7
Suzuki et al. (31)	F/61	Intestinal perforation	Terminal ileum	Peritoneum, stomach, liver, spleen, urinary bladder, direct extension to right diaphragm and lower lobe of lung	DOD at 12 months	Squamous cell carcinoma/ uterine cervix	NA	20
Aitola et al. (7)	F/50	Intestinal obstruction	Terminal ileum	Intra-abdominal spread and retroperitoneal recurrence	AWED at 21 months	Stage I endometrial adenocarcinoma/ uterus	55,6 Gy	14
Aitola et al. (7)	F/78	Bowel obstruction	Jejunum	Abdominal wall and retroperitoneum	DOD at 25 months	Endometrial adenocarcinoma/ uterus	55,5 Gy	10
Policarpio-Nicolas et al. (1)	F/51	Decreased appetite, abdominal pain, increasing abdominal girth	Terminal ileum	Peritoneum, liver, appendix	DOD at 10 months	Stage IIB adenocarcinoma/ uterine cervix	50 Gy	9
Karpeh et al. (20)	NA	NA	Terminal ileum	Recurrent retroperitoneal LNs metastases, widespread pelvic disease, vagina and vulva	NA	Dysgerminoma/ ovary	NA	14
Selk et al. (29)	M/57	Abdominal distension, shortness of breath	Small bowel	Peritoneum and chylous ascites	DOD at 4 months	Chondrosarcoma/ right hemipelvis	NA	8

Table I. *(continued)*

Khalil et al. (2)	M/68	Gastrointestinal bleeding, melena, abdominal pain	Small bowel	Peritoneum, celiac LNs, abdominal wall	DOD at 3 months	30 years history of heavy occupational exposure to radiation and polyvinyl chloride	NA	NA
Navarro-Chagoya et al. (42)	M/45	Gastrointestinal bleeding, melena, weight loss, epigastric pain, fever	Small bowel	Omentum	NA	Unknown pelvic tumor	NA	10
Current case	F/72	Abdominal pain, intestinal obstruction	Terminal ileum	None	ANED at 26 months	Uterine leiomyosarcoma	NK	24

M, male; F, female; NA, not available; NK, not known; AWED, alive with evidence of disease; DOD, dead of disease; ANED, alive with no evidence of disease.

epithelioid hemangioendothelioma, Kaposi's sarcoma (KS), epithelioid gastrointestinal stromal tumor, other sarcomas with epithelioid morphology, melanoma, or a poorly differentiated adenocarcinoma. There is an overlap between epithelioid hemangioendothelioma and epithelioid angiosarcoma. In its pure form, epithelioid hemangioendothelioma is usually composed of cords, strands and solid sheets of vacuolated polygonal to round cells embedded in a myxohyaline matrix, but it lacks of a solid growth pattern generally regarded as a diagnostic clue in favor of epithelioid angiosarcoma [15,25]. The histologic features that help distinguish angiosarcoma from KS are the presence of cavernous vessels and epithelioid endothelial cells in the former and the evidence of both intra-extracellular eosinophilic hyaline bodies and immunoreactivity for HHV-8 in the latter. A vasoformative pattern with evident cytologic atypia and immunoreactivity to CD31 and other endothelial markers would strongly argue against epithelioid GIST. The distinction of PRA from poorly differentiated carcinoma, melanoma, epithelioid leiomyosarcoma and proximal-type epithelioid sarcoma is based on immunohistochemistry. There is overlap in immunohistochemical expression between some epithelioid vascular malignant neoplasms and poorly differentiated epithelial tumors with cytokeratin pools demonstating a membranous and citoplasmic reactivity in both tumor types. It has been suggested that CK19 and CK20 could be useful markers in differentiating epithelioid angiosarcomas from carcinomas, which would be CK19 and CK20 positive [9,11]. Finally, epithelioid angiosarcoma may mimic the angiomatoid variant of epithelioid sarcoma, both in morphology and by the occasional expression of cytokeratin. However, angiosarcoma is more pleomorphic and usually expresses CD31 and Factor VIII.

The standard of care for PRA of the small bowel is complete surgical excision, which is often not possible due to infiltrative and multifocal growth pattern of the neoplasm. Given the rarity of the angiosarcoma of small intestines, there are no large trials that provide guidance for systemic chemotherapy. All adjuvant therapy protocols are empiric and based on studies of soft tissue angiosarcoma that suggest paclitaxel, doxorubicin, docetaxel, and thalidomide therapy may have benefit [3,16,17,51].

In conclusion, primary small bowel angiosarcomas are rarely seen and comprise less than 1% of all intestinal neoplasms. Radiation associated small intestine angiosarcoma might be a special type but with a similar outcome. The pathogenesis of these neoplasms is presumed to be due to irreversible DNA damage. The long latency period associated with these tumors is due to a multistep process involving several dominant gene mutations and deletions that accumulate in the genome over a period of time leading to carcinogenesis. Though the exact molecular mechanisms of carcinogenesis of radiation induced sarcomas are unknown, widely accepted theories include the expression of protooncogene c-jun and inactivation of tumor suppressor genes P53 and Rb. Close long-term surveillance is highly recommended in patients undergoing radiotherapy for the development of secondary malignancies, such as angiosarcomas, in the area of radiation in order to diagnose and treat at early stages.

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