

Development of lymphangiosarcoma after pelvic radiation therapy for uterine cervical cancer: A case report and literature review

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Summary

Angiosarcoma accounts for 1-2% of all soft tissue sarcomas. Common sites of occurrence include the skin, breast, soft tissue, and liver. Angiosarcoma of the gastrointestinal (GI) tract is very rare. We herein present a case of a 41-year-old woman with lymphangiosarcoma of the small intestine occurring 7 years after pelvic radiotherapy for uterine cervical cancer.

Key words: Lymphangiosarcoma; small intestine; cervical cancer; radiotherapy.

Introduction

Angiosarcoma (AS) accounts for only 1-2% of all soft tissue sarcomas [1]. Common sites of occurrence include the skin, breast, deep soft tissue, and liver. AS of the gastrointestinal (GI) tract is very rare [2]. Although its etiology remains unclear, previous studies suggested external-beam irradiation as a cause of AS. We herein present a case of a woman with lymphangiosarcoma (LAS) of the small intestine occurring 7 years after pelvic radiotherapy for uterine cervical cancer. Moreover, through a literature review, we provide current information on the diagnosis and management of LAS.

Case presentation

A 41-year-old Japanese woman with a history of pelvic radiotherapy presented with diarrhea lasting for two weeks and diffuse abdominal pain, distension, nausea, and vomiting that started the previous day. Seven years ago, she had been treated with definitive radiotherapy for FIGO stage IB2 mucinous adenocarcinoma of the uterine cervix. Radiotherapy consisted of whole pelvic external beam radiotherapy (EBRT) followed by high-dose-rate intracavitary brachytherapy (HDR-ICBT). A total pelvic dose of 50 Gy was given in 25 fractions at 5 fractions per week. The total dose of HDR-ICBT prescribed at Point A was 27.2 Gy in 4 fractions. She was regularly followed-up after definitive radiotherapy. Her post-treatment follow-up was uneventful for 7 years without recurrent disease.

On admission, laboratory examinations revealed a white blood cell (WBC) count of $5300/\text{mm}^3$ with 81% neutrophils

and a red blood cell count of $444 \times 10^4/\text{mm}^3$. Her C-reactive protein level was significantly elevated to 0.56 mg/dl (normal range; < 0.4 mg/dl). Although a significant increase was observed in her CA-19-9 level at the time of the initial diagnosis of cervical cancer, her serum CA-19-9 level was normal (23 U/ml, normal range; < 37). Her CA-125 level was also significantly elevated to 254 U/ml (normal range; < 65), but was normal at the initial diagnosis of cervical cancer. Her serum CEA level was normal at 1.1 ng/ml (normal range; < 5).

Abdominal and trans-vaginal ultrasound revealed large ascites formation. Computerized tomographic (CT) scans of the abdomen and pelvis showed dilated small bowel loops with a thickened bowel wall and ascites formation, suggesting bowel obstruction of the small intestine without any evidence of the recurrence of cervical cancer. The site of bowel occlusion was unclear. Her chest X-ray was normal and free air was not detected on abdominal X-ray. A large amount of ascites, but a normal uterus, ovaries, and fallopian tubes were observed on pelvic MRI. Upper endoscopy was normal. Although she developed melena and tarry stools, the site of bleeding was not identified by colonoscopy. However, ^{18}F -fluoro-2-deoxy-d-glucose (FDG) positron emission tomography CT (^{18}F -FDG PET/CT) revealed the diffuse uptake of FDG in the lower abdominal cavity and focal uptake around the right diaphragm, suggesting peritoneal dissemination. A cytological analysis of ascites was positive, suggesting a malignant tumor in the peritoneal cavity. Cultures of ascites were negative. We suspected primary peritoneal cancer or car-



Figure 1. — Resected small intestine showing perforation and tumor nodules.

cinomatous peritonitis from other origins, and exploratory laparotomy was offered to the patient.

Ten days before her planned surgery, the patient developed acute abdominal pain, suggesting panperitonitis. Free air was confirmed by abdominal X-ray, and emergency laparotomy was performed on suspicion of GI tract perforation. Emergency laparotomy revealed a large amount of purulent fluid with grayish white matter in the peritoneal cavity. Her uterus, both adnexa, liver, gallbladder, spleen, and diaphragm were normal. Multiple small nodules suggestive of disseminated tumors were noted on the surface of the greater omentum and sigmoid colon. The small intestinal wall and mesentery were ischemic and necrotic accompanying multiple tumor nodules, with an ileal segment exhibiting perforation. After taking biopsy samples from disseminated tumors, a 15-cm-long segment of the small intestine 3 cm proximal to the terminal ileum was excised (Figure 1), and colostomy was performed.

A histological examination of the small intestine revealed that the mucosa of the small intestine was smooth and there was no ulceration or cancerous lesion. However, severe edema and congestion were noted in the submucosal tissue. Histologically, there were many enlarged vessels between the submucosal layer and serosa (Figure 2 (i)), which contained slightly eosinophilic fluid and a few erythrocytes (Figure 2 (ii)). The wall of the vessel consisted of thin intimal cells and lacked a tunica media. In the subserosal layer, the intima of vessels had large oval nuclei with increased chromatin and papillary proliferation into the lumen. Many small lumens consisting of dense atypical spindle cells were also noted around the enlarged vessels (Figure 2 (iii)). These atypical vessels invaded the submucosal layer and adipose tissue of the mesentery. However, the intima of the normal-sized artery and vein was thin and had no atypia. An immunohistochemical analysis revealed

that the atypical cells were positive for vimentin, CD31, and podoplanin (D2-40), and were negative for CD34, keratin, calretinin, and PAX8, suggesting a lymph vessel origin (Figure 3). We concluded that the patient had LAS.

The postoperative course was complicated by bacterial infection and short bowel syndrome. The following were informed to the patient and her husband: 1) due to the presence of widely disseminated tumors, complete surgical removal was not possible and 2) there are currently no effective adjuvant treatments after initial surgery. She received 3 cycles of nivolumab as off-label use; however, it was ineffective. The patient died of disease progression 7 months after the diagnosis of LAS.

Discussion

We herein described the first case of LAS of the small intestine presenting with intestinal perforation and acute abdomen. The patient had a history of pelvic radiation therapy. Although multimodal treatment, including surgery and immunotherapy, was performed, the patient died of disease progression 7 months after the diagnosis of LAS.

Angiosarcoma (AS) represents 1 to 2% of soft tissue sarcomas and most frequently occurs in the subcutis. Thus, intra-abdominal AS is a very rare neoplasm that generally occurs in the liver or spleen, and, in extremely rare cases, the GI tract [3]. In a review that included 106 cases of GI vascular tumors treated at the Mayo Clinic between 1925 and 1944, only 14 cases of AS were found: 7 in the stomach, 3 in the small intestine, 2 in the rectum, 1 in the esophagus, and 1 in the appendix [4].

LAS is AS with prominent lymphatic differentiation that arises from lymphatic endothelial cells. The classic microscopic appearance of LAS is a network of anastomosing, delicate vascular channels lined by atypical endothelial cells. However, a morphological diagnosis is sometimes

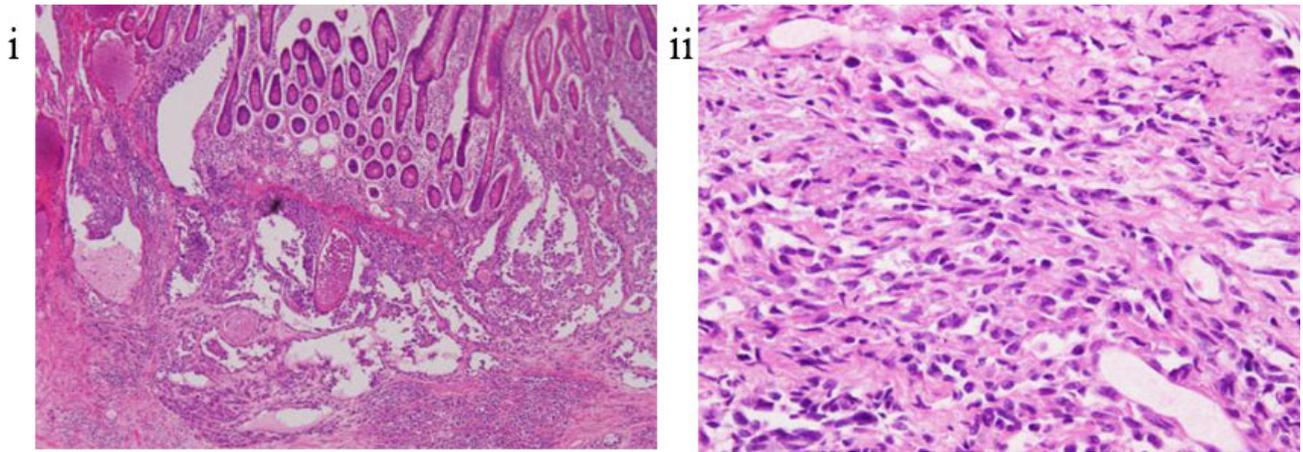


Figure 2. — Histopathological analyses of the removed small intestine. (i) Enlarged vessels observed in the submucosal tissue (Hematoxylin and eosin staining; 20× magnification). (ii) Small lumens consisted of dense atypical spindle cells around the enlarged vessels. Eosinophilic fluid and erythrocytes observed in the enlarged vessels (Hematoxylin and eosin staining; 200× magnification).

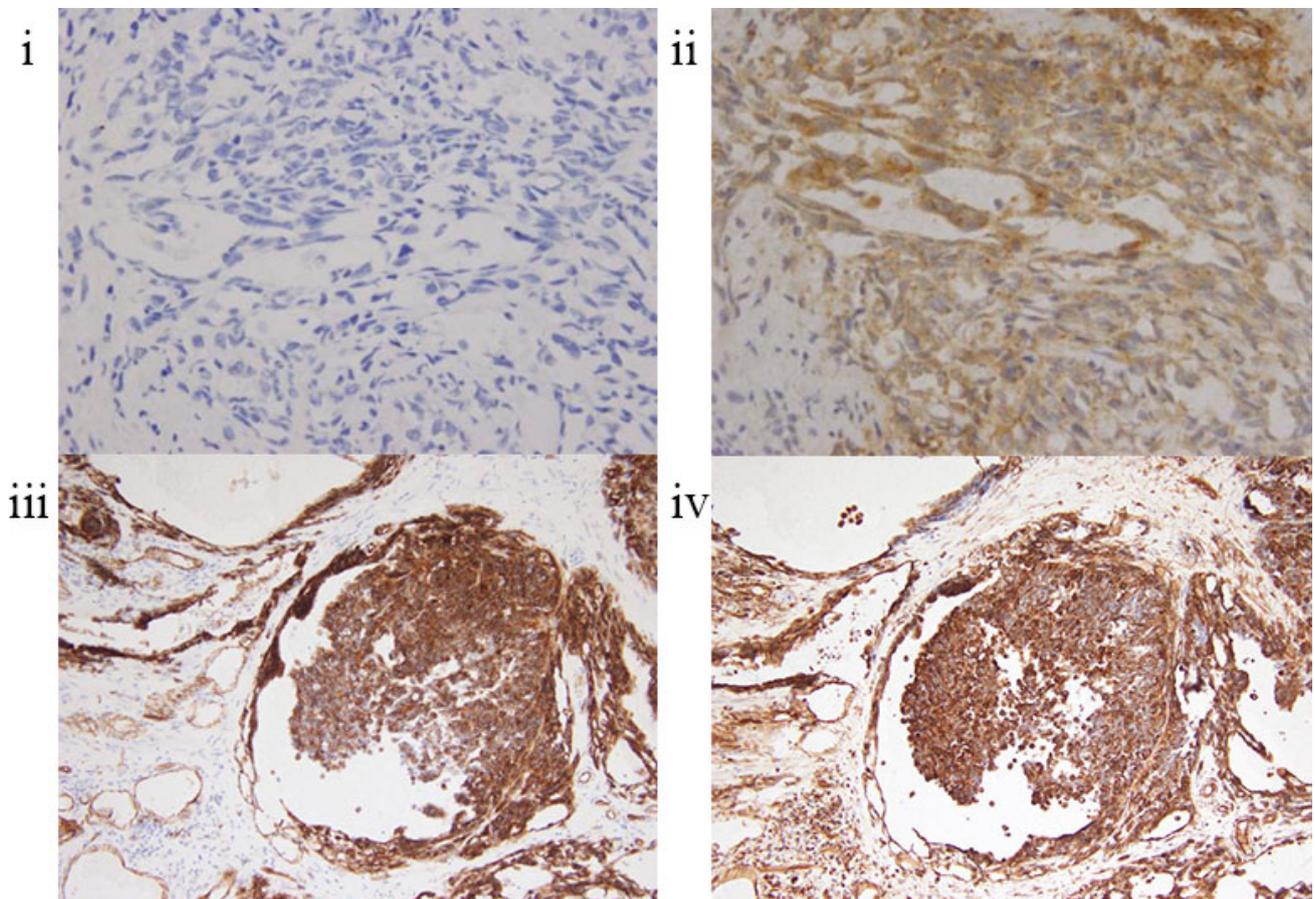


Figure 3. — Immunohistochemical analyses of the tumor. (i) Immunoreactivity for cytokeratin AE1/AE3 (200× magnification). (ii) Immunoreactivity for D2-40 (200× magnification). (iii) Immunoreactivity for CD31 (200× magnification). (iv) Immunoreactivity for vimentin (200× magnification)

challenging when differentiating a vascular neoplasm from an epithelial neoplasm, such as poorly differentiated carcinomas. Moreover, due to close histological and embryogenetic relationships, difficulties are associated with differen-

tiating between malignant vascular tumors of blood vessels (AS) and of a lymph vessel origin (LAS) based solely on morphology. Enzinger and Weiss stated that "as it is usually impossible to determine which tumors display lymphatic

Table 1. — Reported cases of post-radiation angiosarcoma arising in the small intestine.

Authors Year (Reference)	Age /Sex	Immunoreactivity	AS/LAS		Previous radiotherapy				
			Location	Survival	Treatment	Irradiated tumor	Radiation dose	Time from RT to AS/LAS	
Chen et al. 1979 [23]	66/Female	NA	AS: Small intestine (terminal ileum)	14 months	Surgery		Ovarian cancer	60 Gy	8 years
Nanus et al. 1987 [24]	42/Female	NA	AS: Small intestine (terminal ileum)	36 months	Surgery		Ovarian dysgerminoma	48 Gy	16 years
Wolov et al. 1991 [25]	80/Female	Factor VIII-related antigen	AS: Small and large intestines	23 days	Surgery		Cervical cancer	55 Gy	20 years
Wolov et al. 1991 [25]	69/Female	Factor VIII-related antigen	AS: Small and large intestines	3 weeks	Surgery		Endometrial cancer	50 Gy	7 years
Berry et al. 1991 [26]	51/Male	Ulex Europaeus Agglutinin 1 Vimentin	AS: Small intestine (terminal ileum)	5 months	Surgery	Adriamycin +dacarbazine	Hodgkin's lymphoma	NA	3 years
Su et al. 1991 [27]	48/Female	Factor VIII-related antigen Ulex Europaeus Agglutinin 1	AS: Small intestine (terminal ileum)	23 days	Surgery		Cervical cancer	NA	3.2 years
Hwang et al. 1993 [28]	60/Female	Ulex Europaeus Agglutinin 1	AS: Small intestine	2 months	Surgery		Cervical cancer	96.5 Gy	8 years
Hansen et al. 1996 [29]	76/Female	Factor VIII-related antigen Vimentin	AS: Small intestine	5 months	Surgery		Endometrial cancer	45.1 Gy	7 years
Suzuki et al. 1999 [15]	61/Female	Factor VIII-related antigen Ulex Europaeus Agglutinin 1	AS: Small intestine (terminal ileum)	12 months	Surgery	Cisplatin	Cervical cancer	NA	20 years
Aitola et al. 1999 [30]	50/Female	CD31 CD34 Factor VIII-related antigen	AS: Small intestine (terminal ileum)	21 months	Surgery	Doxorubicin	Endometrial cancer	55.6 Gy	14 years
Aitola et al. 1999 [30]	78/Female	Factor VIII-related antigen CD31 CD34 Ulex Europaeus Agglutinin 1	AS: Small intestine (jejunum)	24 months	Surgery		Endometrial cancer	55.5 Gy	10 years
Selk et al. 2004 [31]	57/Male	NA	AS: Small intestine	4 months	Surgery		Chondrosarcoma of the pelvis	NA	8 years
Khalil et al. 2005 [32]	68/Male	CD31 CD34 Vimentin	AS: Small intestine (Ileocecal)	6 months	Surgery		Occupational radiation exposure	NA	30 years
Policarpio-Nicolas et al. 2006 [17]	51/Female	CD31 CD34 Factor VIII-related antigen	AS: Small intestine (terminal ileum)	10 months	Surgery		Cervical cancer	50 Gy	9 years
Navarro-Chagoya et al. 2015 [33]	45/Male	CD31 Cytokeratin AE1/AE3 Factor VIII-related antigen	AS: Small intestine (ileum and jejunum)	NA	Surgery		Unknown pelvic tumor	NA	10 years
Present case	41/Female	CD31 CD34 Vimentin D2-40	LAS: Small intestine (terminal ileum)	7 months	Surgery	Nivolumab	Cervical cancer	50 Gy	7 years

AS, angiosarcoma; LAS, lymphangiosarcoma, SCC, squamous cell carcinoma; NA, not available; RT, radiotherapy.

versus vascular differentiation, all are referred to as AS, even those that arise in the setting of lymphedema.”[5]. Thus, pathologists have used the term AS to encompass both AS and LAS. However, the recent development of new immunohistochemical markers suggests that LAS may be defined immunophenotypically. Typical LAS is positive for the mesenchymal marker vimentin, endothelial markers (e.g., CD31 and CD34), and markers of the lymphatic endothelium (e.g., D2-40, Prox-1, LYVE-1, and VEGFR receptor-3 (VEGFR-3)), but negative for the epithelial marker cytokeratin [6].

Although the etiology of AS/LAS is unclear, several factors have been implicated in its pathogenesis, including occupational exposure to certain toxins (e.g. vinyl chloride, thorotrast, or arsenic) [7], a chronic lymphedematous extremity (e.g. Stewart-Treves syndrome, Milroy’s disease, and chronic filaria) [8,9], external-beam irradiation [10], trauma, and the prolonged retention of a foreign body [11]. The present case had a history of pelvic radiotherapy.

Common post-radiation vascular tumors include undifferentiated pleomorphic sarcoma, LAS, hemangiosarcoma, leiomyosarcoma, and fibrosarcoma [12]. Post-radiation AS/LAS generally occurs after an interval of 5-11 years following irradiation for carcinoma of the breast, ovary, uterus, and cervix [13]. The dose of prior radiation ranged between 4000 to 8000 rad [14]. In the present case, LAS developed 7 years after pelvic radiotherapy for uterine cervical cancer.

Post-radiation AS has been reported in the omentum, small intestine, and colon, and in the form of diffuse AS in the entire abdomen [15]. In the present case, LAS developed in the small intestine. The small intestine constitutes approximately 75% of the GI tract; however, only between 1 and 1.6% of all GI malignant tumors originate at this site [16]. As shown in Table 1, to the best of our knowledge, there have only been 16 cases of post-radiation AS arising in the small intestine, including ours, demonstrating the extreme rarity of this condition. Of these, 6 cases were post-radiation AS that occurred following irradiation for cervical cancer [17]. Since previous case series did not conduct immunostaining using lymphatic vessel markers, the present case is the only case of post-radiation LAS arising in the small intestine (Table 1).

Clinically, malignant tumors of the small intestine generally present with GI bleeding, anemia, and intestinal obstruction. Due to their non-specific clinical presentation, most often with GI bleeding and anemia, a diagnosis is only reached after an extensive search. In the present case, symptoms were abdominal pain and bowel obstruction, and the time from the initial consultation to the day of surgery was 74 days.

AS has been treated using a multimodal approach. Although complete surgical resection is considered to be the only effective treatment, complete surgical excision is often not possible due to the infiltrative and multifocal nature of this malignancy. Chemotherapy, radiotherapy, and

their combination have been attempted for these patients [18, 19]. However, there is currently no consensus on the effectiveness of chemotherapy or radiotherapy. Commonly employed anti-cancer agents have been cisplatin, taxanes, ifosfamide, gemcitabine, and anthracyclines [20]. More recently, the use of biologic agents, such as sorafenib, sunitinib, and bevacizumab, has also been reported [15, 21]. However, no survival benefit of these therapeutic regimens has been demonstrated. According to previous studies, the overall 5-year survival rate for patients with AS/LAS is 20-35% [16, 22]. As shown in Table 1, most patients with AS/LAS of the small intestine after radiotherapy died within one year of diagnosis (Table 1). Among the 15 cases for which survival times were available, the one-year survival rate after diagnosis was only 33.3%. All patients with post-radiation AS/LAS with a history of cervical cancer died within one year (Table 1). Our patient attempted the featured checkpoint inhibitor nivolumab as off-label use; however, it was ineffective. Thus, a novel effective treatment is urgently required for this disease.

In summary, we herein reported the first case of post-radiation LAS in the small intestine. Although AS/LAS of the small intestine is extremely rare, it needs to be considered in patients with a history of radiotherapy. Due to the rarity of LAS, we consider it to be of great importance to report even individual cases in order to establish an optimal treatment.

Author contributions

HU, SM and TW wrote the manuscript. IA performed the research. SY performed review & editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Informed consent was obtained from the patient for publication of this case Report.

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Conflict of interest

The authors declare no competing interests.

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