CASE REPORT

Radiation-associated peritoneal angiosarcoma

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SUMMARY

Angiosarcomas account for only 1–2% of all soft tissue sarcomas, with the most common site of origin being in the head and neck region. Peritoneal angiosarcoma is an extremely rare tumour and few cases have been reported previously. Presentation of peritoneal angiosarcoma can be very variable, hence making diagnosis difficult. Herein, we review the current literature and describe a rare case of a patient who presented with haemorrhagic ascites, 17 years after radiotherapy for endometrial carcinoma and was subsequently diagnosed with peritoneal angiosarcoma. Due to extensive disease, surgery was not a viable option. She was started on palliative chemotherapy, but despite treatment, her condition deteriorated further and she eventually passed away. We highlight the diagnostic challenges and considerations in these patients as well as current treatment and management options available.

BACKGROUND

Sarcomas are malignant tumours that arise from mesenchymal cells, accounting for 1% of all adult malignancies.¹ They comprise various histopathologies, with angiosarcomas making up only 2% of all sarcomas.¹ Angiosarcomas arise from the endothelial layer of vascular elements and occur most commonly in the head and neck region.² They can arise primarily or secondarily due to previous radiation or in long-standing lymphedema (Stewart-Treves syndrome), chronic infection, chronic usage of chemical agents (eg, steroids, vinyl chloride, arsenic medication) or trauma. Radiotherapy (RT) leads to secondary angiosarcoma in <1% of patients receiving RT³ and has been reported in multiple sites, for example, skin, breast, bone and the gastrointestinal tract. Here we present a rare case of a patient who developed peritoneal angiosarcoma 17 years after RT for endometrial carcinoma.

CASE PRESENTATION

The patient is a middle-aged woman who suffered from stage 3C endometrial carcinoma in the late 1990s. She underwent a total hysterectomy and bilateral salpingo-oophorectomy, followed by RT and brachytherapy. She was discharged from oncological follow-up and had been asymptomatic until her recent presentation.

Seventeen years later, the patient presented to our surgical oncology clinic with a 1-month history of abdominal distension, bloatedness and bilateral lower limb swelling. This was associated with weight loss of 4 kg in 1 month. She did not have any

other significant gastrointestinal or urinary tract symptoms. On physical examination, her abdomen was distended with ascites and there were no palpable masses, digital rectal examination revealed fullness in the pouch of Douglas but no mucosal abnormalities. Vaginal and speculum examination did not reveal any abnormalities. She underwent laboratory and radiological investigations, and her cancer antigen 125 levels was found to be elevated at 99 (normal <35.1 U/mL). Ultrasound duplex of her lower limbs did not show any evidence of deep vein thrombosis. She proceeded to have a CT scan of her abdomen and pelvis which showed a rim-enhancing fluid collection in the pelvis, with peritoneal and omental nodularity, and ascites. These findings were suspicious for peritoneal metastasis. Her CT chest showed no thoracic lesions. The fluid collection was re-evaluated with an MRI scan, which showed a 8.0×7.8×7.9 cm cystic mass situated atop the vaginal stump with thick enhancing walls (figure 1A,B). Her case was discussed at our multidisciplinary tumour board (MDT) meeting consisting of radiologists, radiation oncologists, medical oncologists, pathologists and surgical oncologists. The MDT recommendation was for a transrectal biopsy of the pelvic lesion.

Colonoscopy was performed, and this showed signs of radiation proctitis. An endoscopic ultrasound confirmed the cystic nature of the mass and an aspiration till complete collapse of the mass was performed. One hundred millilitres of reddish-brown fluid was aspirated in total and sent for culture and cytology. The fluid culture returned as positive for salmonella, and cytology was negative for malignancy. The patient was referred to the Infectious Disease physician and treated for salmonella infection with ciprofloxacin 500 mg twice a day, for 7 days. A repeat ultrasound pelvis done a week after, to document complete resolution of the collection, showed a recurrent 7.0 cm fluid collection. Clinically, the patient continued to be intermittently febrile. In view of the sizeable collection, she was underwent a CT-guided transgluteal drainage, during which the collection was drained completely. One month later, her tumour markers had normalised to 20.2 U/mL and she remained well. A repeat CT scan a month later (figure 2) showed an interval reduction from 8 cm to 4 cm and complete resolution of the fluid collection in 2 months (figure 3).

However, 5 months after initial presentation, the patient again presented with abdominal distension and bilateral lower limb swelling. A repeat CT of her abdomen and pelvis was performed (figure 4), which showed increased ascites compared with the

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Figure 1 (A, B) Axial and sagittal views showing the cystic mass situated atop the vaginal stump with thick enhancing walls, which was aspirated via endoscopy.

CT scan done 3 months prior. Her scan was discussed at the MDT and the recommendation was for ascitic tap by interventional radiology (IR). She had an uncomplicated procedure done a week after the scan and IR was able to aspirate 45 mL of heavily blood-stained fluid. The cytology of the fluid was negative for malignancy. During follow-up a week after the ascitic tap, her haemoglobin level was found to have dropped to 7.9 g/dL from 10.2 g/dL. She was admitted and transfused three units of packed cells. In view of the negative ascitic tap yield and the recurrent drops in haemoglobin levels, she was offered a diagnostic laparoscopy, for which she agreed.

Diagnostic laparoscopy was performed a month later. Intraoperatively, 5.4 L of haemorrhagic ascites was drained and a fibrinous film covering her entire peritoneal cavity was seen, with a few whitish nodules along the liver edge. The peritoneal fluid was sent for cytology and only showed atypical mesothelial cells favouring reactive changes. Multiple biopsies of the peritoneum and tissue over the liver were taken but were negative for malignancy (figure 5). Her case was again discussed at the MDT, and the consensus was for expectant management in view of the negative results. She recovered uneventfully and was discharged with a stable haemoglobin level at 9.3 g/dL. She was advised for close monitoring of her symptoms and haemoglobin levels and was seen in clinic 1 month later.

Figure 2 Interval decrease in size of collection on follow-up imaging from 8 cm to 4 cm.

Figure 3 Interval resolution of the collection above the vaginal stump.

Unfortunately, she presented again with abdominal distension and symptomatic anaemia 1 month after undergoing the diagnostic laparoscopy, before her clinic appointment. Her haemoglobin level was found to have dropped to 5.6 g/dL. Again, she received three units of packed cells and underwent a CT mesenteric angiography and a red cell tag scan. This did not localise the source of bleeding but showed increased amounts of ascites. As she was symptomatic from the abdominal distension, she underwent an urgent ultrasound-guided drainage of the ascites. After drainage of her ascites, her haemoglobin level was found to have dropped to 6.6 g/dL and she received another five units of packed red cells. In view of her recurrent bloody ascites and unstable haemoglobin level, the decision was made to proceed with an exploratory laparotomy.

During the laparotomy, 4.5 L of haemorrhagic ascites was drained. The entire peritoneal cavity was covered with a thick fibrinous tissue (figure 6). Multiple biopsies were taken and the histology confirmed a peritoneal angiosarcoma. The histology slides were reviewed by a sarcoma pathologist, and the lesional cells were positive for CD31, c-Myc and FVIII (patchy and

Figure 4 Interval increase in ascites but no significant masses or collections noted.

Figure 5 Fibroadipose tissue with scattered inflammatory cells reactive fibrosis. No malignancy present.

weak), MNF116 and INI1 (figure 7). As the disease was locally extensive in the peritoneum, surgical treatment was not feasible and the decision was made for palliative chemotherapy. She was referred to the medical oncologist and counselled for chemotherapy, subsequently starting on doxorubicin.

OUTCOME AND FOLLOW-UP

Despite initiation of chemotherapy, the patient continued to suffer with persistent haemorrhagic ascites and bleeding, and required repeated blood product transfusions. The source of her bleeding was not amenable to embolisation or surgical intervention. Her condition was further complicated by peritonitis and a neutropenic state for which she received granulocyte-colony stimulating factor. After extensive discussions regarding the limited options for further medical treatment, the patient decided for best supportive care. The palliative care team was engaged for symptomatic control and she passed away at home 2 weeks after discharge.

DISCUSSION

Angiosarcoma is an extremely rare tumour, making up 2% of all soft tissue sarcomas and carries a poor prognosis.¹ It can be classified into either primary (arising de novo) or secondary angiosarcoma from previous radiation, trauma, chronic lymphedema

Figure 6 Exploratory laparotomy showing fibrinous tissue covering peritoneum.

Figure 7 Histology slide showing dyscohesive clusters of large epithelioid cells embedded in a haemorrhagic and fibrin-rich stroma. These cells show large pleomorphic nuclei, prominent nucleoli and pale vacuolated cytoplasm. The tumour cells immunostain positively for the endothelial marker CD31. Immunostains for keratins, mesothelial and macrophage markers are negative, confirming the diagnosis of angiosarcoma.

or chronic infection. Of all angiosarcoma cases, only a handful of disseminated peritoneal angiosarcoma cases were reported.⁴

Being an invasive and aggressive tumour, angiosarcomas exhibit early hematogenous and lymphogenous dissemination, resulting in a median survival period of 8 months.¹ Cahan *et al*⁵ initially proposed a series of criteria to help diagnose secondary postradiation sarcomas arising in bone, which was later modified by Arlen *et al*.⁶ These included (1) histological confirmation of sarcoma with differing histology between the sarcoma and the primary tumour, (2) the tumour must originate from an area covered by previous radiation and (3) the latency period must be sufficiently long (at least 3 years).

Peritoneal angiosarcomas are very rare, with an incidence of 0.01% per 100 000 patients^{7 8} with only a few case reports available. One such case report was of disseminated peritoneal angiosarcoma that occurred 20 years after treatment for ovarian cancer with RT.⁹ Other such case reports include that of small bowel angiosarcoma and greater omentum angiosarcoma.^{7 10} The clinical presentations of patients with peritoneal angiosarcomas are diverse and non-specific. These include abdominal distention, symptomatic malignant ascites or occasionally patients may present with a perforated viscus or intestinal obstruction.⁷ Due to these non-specific symptoms, patients tend to be diagnosed at an advanced stage. Furthermore, a definitive association between radiation and intra-abdominal angiosarcoma is difficult to establish, and the latent time interval between RT to diagnosis of peritoneal angiosarcoma tends to be longer compared with that of breast secondary angiosarcoma (15–20 years vs 6–7 years, respectively).^{11–13}

Despite treatment, progression of disease usually occurs and patients will succumb within a year of diagnosis.^{7 10 14 15} Certain prognostic factors have been proposed, such as the size of the lesion, with better outcome for lesions measuring <5 cm.¹⁶ Absence of lymphocytic infiltrate and a high histological grade represents a poorer prognosis.¹⁷ Some studies done to compare primary and postradiation angiosarcoma showed that a history of prior radiation was not a significant prognostic factor.¹²

Evidence-based recommendations for the treatment of angiosarcomas are scarce. Currently, the gold standard for management of patients with radiation-induced angiosarcoma is radical resection, that is, en bloc resection with negative margins, for a potentially curable localised disease.^{12 18 19}

Wide surgical resection with microscopically negative margins significantly improves overall survival compared with those who had microscopically positive margins (median survival of 4.9 ± 1.1 years compared with 2.0 ± 0.4 years, respectively).²⁰ This should then be followed by adjuvant RT to prevent local recurrence.²¹ Beuhler *et al* observed a decrease in local recurrence rate and prolonged time interval to local recurrence in patients who underwent surgical resection followed by adjuvant radiation for localised disease, where the median overall survival is 47 months compared with 10 months in non-irradiated patients.¹² In addition, the Riad series showed that the risk of local recurrence was significantly lower in patients with radiation-induced angiosarcomas even if they were reirradiated after surgical treatment.²²

Systemic chemotherapy can be considered for inoperable, locally advanced or metastatic angiosarcomas. Doxorubicin and paclitaxel are the two most common agents being used; however, disease response has been variable.^{20 23–26} Pegylated-liposomal doxorubicin is another option to avoid doxorubicin-based chemotherapy toxicity in metastatic soft tissue sarcoma.²⁰ Few small studies on the efficacy of pegylated-liposomal doxorubicin and paclitaxel had been done and would require further investigation to determine the doses and schedule of chemotherapy regimens for optimal results. Hillenbrand *et al*²⁷ showed complete remission under treatment with pegylated-liposomal doxorubicin for two patients while treatment with paclitaxel had a mixed response in two patients (each with one primary and one secondary angiosarcoma). Skubitz and Haddad also demonstrated the use of pegylated-liposomal doxorubicin and paclitaxel in six patients showing clinical benefit in treatment of angiosarcomas with low toxicity profiles.²⁸ So, further studies with a bigger sample size would be needed to elucidate which would be the first-line therapy as well as the benefit of combination therapy.²⁶

Recently, the use of antiangiogenic therapy such as sorafenib has been used with mixed response.^{28 29} Maki *et al* studied the efficacy of sorafenib in 145 patients with metastatic or recurrent sarcomas and found that it is more active in patients with secondary angiosarcoma as opposed to patients with primary angiosarcoma.²⁹ In a phase II trial from the French Sarcoma Group (GSF/GETO) with 41 patients with advanced angiosarcoma, sorafenib showed a response rate of 23% in chemotherapeutic population whereas chemotherapy-naïve patients had no response.²⁸

At the molecular level, secondary angiosarcomas are differentiated from primary angiosarcomas in their pathogenesis by showing significantly higher levels of MYC (a regulator gene that codes for a transcription factor) amplification as well as FLT4 (VEGFR3).^{11 30–32} Hence, MYC amplification can be an additional diagnostic tool when postradiation angiosarcoma is being investigated.³³ This then provides another potential pathway for the treatment of this condition.

In our case, we reached the diagnosis of locally advanced angiosarcoma of the peritoneum after 7 months of extensive investigations. Unfortunately, the disease was very advanced and thus deemed unsuitable for surgical resection, either for curative or palliative purposes. The diagnosis was challenging as fluid cytology were benign and biopsies from her first diagnostic laparoscopy showed only fibrofatty tissue and staining

with AE1/3 did not highlight the presence of any carcinoma cells. The diagnosis was clinched where biopsies from the second surgery showed cells with enlarged, irregular, vesicular nuclei and pale cytoplasm and an extensive range of immunohistochemistry was carried out. She was subsequently treated with systemic chemotherapy but had limited response to the treatment, coupled with rapid deterioration.

Learning points

- ▶ Peritoneal angiosarcoma is a rare and aggressive condition, which usually presents with non-specific abdominal symptoms and is hence often diagnosed late.
- ▶ Diagnosis is difficult and should always be considered when a patient with a background of previous radiotherapy to abdominal or pelvic organs with a latent period of >10 years presents with haemorrhagic ascites.

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