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Case report

Synovial sarcoma of the vulva: A case report and literature review with discussion on fertility sparing approaches

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1. Introduction

Synovial sarcoma is a relatively rare sarcoma accounting for 5–10% of all soft tissue sarcomas, typically afflicting young to middle aged adults. (Gazendam et al., 2021) These have the capacity to occur in a wide variety of anatomic sites including the female genital tract. (Kolin et al., 2020) Morphologically, synovial sarcomas are divided into two major subtypes; monophasic, which is composed of either epithelial or spindle cell components, and biphasic, which is composed of both epithelial and spindle cell components. There is also a less common third histologic subtype; poorly differentiated. (Gazendam et al., 2021).

Unfortunately, diagnosis of synovial sarcoma can be challenging. While ultrasound is often the first-line investigation, synovial sarcoma is best evaluated with magnetic resonance (MR) imaging. (Wang et al., 2021) However, as described by Wang et al., MR appearance of synovial sarcoma can be quite diverse including homogenous solid lesions, pure cystic lesions as well as mixed solid and cystic lesions. (Wang et al., 2021) Most commonly synovial sarcoma will present as aggressive appearing, heterogeneous masses with hemorrhagic and cystic foci with or without calcifications; however, in up to one third of cases, lesions will instead appear more benign and are homogeneously solid or cystic. (Wang et al., 2021).

Pathologic diagnosis can also be challenging. The differential diagnosis for disease within the vulvovaginal region includes carcinosarcoma or spindle cell epithelioma for biphasic lesion as well as squamous cell carcinoma, melanoma, smooth muscle tumors, MPNST, angiomyxoma, or solitary fibrous tumor for monophasic lesions. (Kolin et al., 2020; Sumathi et al., 2011) For poorly differentiated malignancy, the differential can include lymphoma, melanoma, Ewing sarcoma, poorly differentiated carcinoma, synovial sarcoma and alveolar rhabdomyosarcoma. (Kolin et al., 2020).

The pathognomic translocation to confirm a diagnosis of synovial sarcoma is t(X:18), which is present in > 95% of cases. (Gazendam et al., 2021) This leads to the fusion of SS18, a gene on chromosome 18, with either SSX1, SSX2, or SSX4 on the X chromosome. (Sumathi et al., 2011) SS18/SSX1 is the most common fusion. (Sumathi et al., 2011).

The mainstay of curative intent treatment for patients with localized disease is surgical resection with widely negative margins with or without addition of chemotherapy or radiation therapy. (Gazendam et al., 2021; Wang et al., 2021) Compared to other soft-tissue sarcomas, synovial sarcoma is relatively chemosensitive. (Gazendam et al., 2021; Wang et al., 2021) Use of neoadjuvant or adjuvant systemic agents is better established in pediatric patients and the most used systemic agents are ifosfamide and doxorubicin; however, the role in the adult population is not as clear. (Gazendam et al., 2021).

As for the role of radiation, while prior retrospective work has shown that that addition of radiation can improve cancer control outcomes such as local-recurrence free survival and progression free survival, it is

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not indicated for all patients. (Song et al., 2017; Palmerini et al., 2009; Network and Guidelines, 2022) Some common consideration for addition of radiation include stage III disease as well as close or positive surgical margins that cannot be re-resected. (Network and Guidelines, 2022) It can also be considered for those with stage II disease. (Network and Guidelines, 2022).

Depending on the location of the primary tumour, the toxicities associated with radiation can vary significantly. Specifically, when delivering radiation to the pelvis, fertility and gonadal function can subsequently become impaired. Some established methods of fertility preservation for female patients requiring pelvic radiation include embryo or oocyte cryopreservation and ovarian transposition. (Ghadjar et al., 2015) These are viable options for many patients; however, they can introduce a time delay and not all patients are eligible or wish to undergo these invasive procedures. Individualization is imperative for fertility preservation in young female patients who receive pelvic radiation.

Here we discuss the case of patient with synovial sarcoma of the vulva who maintained fertility following adjuvant radiation therapy. This is case report is accompanied by a review of the relevant literature.

2. Case presentation

A 36-year-old G2T1P0A1L1 woman presented with a 3-month history of left vulvar swelling, initially less than 1 cm, but eventually progressing to about 4–5 cm in diameter. Physical exam showed a 5 cm mobile mass of the left vulva with no other masses or lymphadenopathy identified. The remainder of the physical exam was normal.

Ultrasound of the mass showed a heterogenous, lobulated solid lesion with well circumscribed margins measuring 3.4 × 2.3 × 4.2 cm with internal vascular flow on Doppler. MR imaging of the lesion was done revealing a well-demarcated 3.1 × 4.7 × 2.7 cm lesion with intermediate T1 and T2 weighted signal and a high T2 weighted signal intensity rim along the margin. It was not reported as obviously malignant and based on the pre-operative imaging, she underwent excisional biopsy with a general gynecologist. This was tolerated well with no complications.

Initial pathology was reported as 'biphasic lesion' with a large differential including metastatic endometrioid adenocarcinoma or Mullerian adenosarcoma. However, a subsequent pathology review was conducted at our institution, leading to a diagnosis of biphasic synovial sarcoma. Histology showed a biphasic tumour, consisting of both epithelial and spindled cell components, that had a high mitotic rate of $>$ 40 mitoses/10HPF. Fluorescence in situ hybridization (FISH) testing was conducted revealing a hybridized pattern of SS18:SSX chromosome translocation consistent with synovial sarcoma. (Gazendam et al., 2021) Given how the specimen was resected, surgical margins could not be assessed.

Given the uncommon pathology, she was then referred to our tertiary cancer care center. CT imaging of the chest, abdomen, and pelvis was conducted showing no evidence of disease spread. However, on exam there remained a palpable thickening around the surgical scar.

She underwent re-excision of the vulvar scar for wide margins. Pathology from the re-excision showed a 0.5 mm focus of residual disease with negative surgical margins; however, an exact margin size could not be determined as the section with tumor did not contain an inked margin. Given the unclear surgical margin, the options of careful surveillance versus adjuvant radiation were considered and discussed with the patient, and ultimately a decision was made to proceed with radiation. She was treated with adjuvant external beam radiation (EBRT), 50 Gy in 25 fractions everyday Monday to Friday which started 6 weeks after surgery. Her radiation was given using an IMRT (Intensity-Modulated Radiation Therapy) approach, which, compared to older radiation planning techniques, allows for more modulation of the dose distribution. (Elith et al., 2011) This enabled good coverage for the target tissues while minimizing dose to nearby organs. (Elith et al., 2011).

During radiation planning, dose hot spots in the uterus, rectum, and bowel were avoided and dose to the ovaries was minimized. Specifically, the mean dose to each ovary was minimized as much as possible without compromising dose to the target volume. The radiation doses that the ovaries and the uterus received can be found in Table 1. All other organs at risk met our institutional constraints. Fig. 1 shows the final radiation treatment plan.

Our patient already had one child. Prior to her cancer diagnosis she had expressed the wish to have a second, but after her diagnosis this was not a high priority for her. Nevertheless, three months after completing radiation our patient did become pregnant. She was initially hesitant to proceed with the pregnancy due to concerns over potential teratogenic effects from her recent radiation. However, as treatment was completed prior to conception we were able to reassure her that this would be an accepted risk. She was immediately referred to be seen by High-Risk Obstetrics for counseling and access to specialized care. She ultimately decided to proceed with the pregnancy and went on to have an uncomplicated pregnancy and delivery of a healthy baby. She continues to do well and is now over two years from her treatment with no evidence of recurrence on imaging or clinical exam.

3. Discussion

3.1. Management of vulvar synovial sarcoma

Review of the literature identified four papers describing six separate cases of vulvar synovial sarcoma. The clinical details of these cases are outlined in Table 2. Studies without any information regarding receipt of adjuvant therapy were not included. Of these six reported cases, 3 were biphasic and 3 were monophasic. All patients were treated with up-front resection. As for adjuvant treatment, 2 patients received adjuvant radiotherapy alone, 1 received both adjuvant radiation and chemotherapy, 1 received adjuvant chemotherapy alone, and 1 did not receive any adjuvant therapies.

For case 3, adjuvant doxorubicin and ifosfamide was given based on the known relative chemosensitivity of synovial sarcoma and the morbidity of recurrent disease in the vulvar region. (Holloway et al., 2007) The other patient who received systemic therapy, case 4, was treated with carboplatin and paclitaxel because initial diagnosis was of endometrioid carcinoma, which highlights the difficulties in pathologic diagnosis of synovial sarcoma described earlier. (Kolin et al., 2020) While the role of chemotherapy in adult patients with synovial sarcoma remains unclear, the current evidence is described well by Gazendam et al. in their recent review. There is no specific guidance in the literature as far as the role of systemic agents for vulvovaginal disease.

As for the role of radiation, there is evidence supporting improved cancer control with the addition of radiation in the management of synovial sarcoma. (Song et al., 2017) In their retrospective analysis, Song et al. found that adjuvant radiation increased the local-recurrence free survival (HR: 0.195, 95%CI: 0.046–0.838, p = 0.028) and progression-free survival (HR: 0.248, 95%CI: 0.092–0.671. p = 0.006). (Song et al., 2017) Another single institution, retrospective analysis by Palmerini et al., found similar results with omission of radiation leading to decrease in event-free survival (HR: 1.86, 95% CI: 1.09–3.17, p = 0.02). (Palmerini et al., 2009).

With respect to follow-up duration, the available studies are variable. Our follow-up in this case is short so far at 2-year post-treatment. However, she continues to be followed closely for both local and

Table 1
Summary of radiation doses to reproductive structures.

Location	Average Dose (Gy)	Maximum Dose (Gy)
Left Ovary	2.30	5.18
Right Ovary	1.28	1.99
Uterus	7.99	40.12

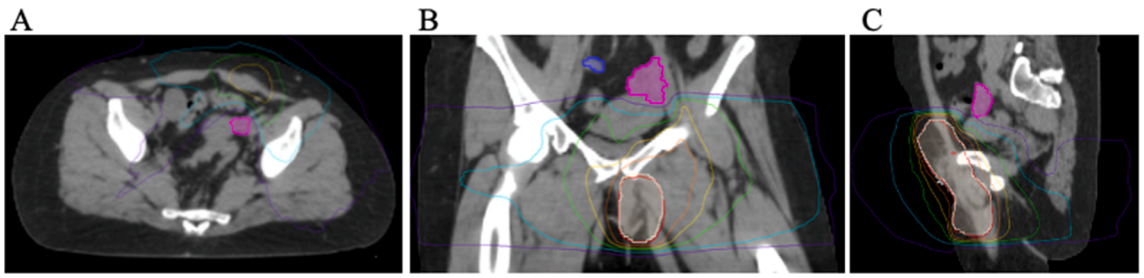

Fig. 1. Radiation treatment plan shown in axial (a), coronal (b) and sagittal (c) views. Left ovary is outlined in magenta and right ovary in blue. Target treatment volume (i.e planning target volume or PTV) is outlined in cream. Representative dose lines are shown; 50 Gy (red), 40 Gy (orange), 30 Gy (yellow), 20 Gy (green), 10 Gy (light blue), 5 Gy (dark blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Summary of previously reported cases of vulvar synovial sarcoma.

Case No.	Age (yr)	Size (cm)	Morphology	Surgical Excision	Final Surgical Margins	Adjuvant Treatment	Outcome
1 (White et al., 2008)	33	5	Monophasic	Yes; Partial radical vulvectomy with rotational flap vulvoplasty	Negative but close at deep margin (no measurement given)	No adjuvant treatment given	Lymph node recurrence at 1.2 yr, ANED at 2.5 yr
2 (Asher et al., 2011)	28	2.2	Biphasic	Yes	Negative	No adjuvant treatment given	ANED at 3.0 yr
3 (Kolin et al., 2020; Holloway et al., 2007)	50	4.2	Monophasic	Yes	Positive	Neoadjuvant external beam radiation (IMRT, 50.4 Gy in 28 fractions) with adjuvant brachytherapy boost (total dose of 18 Gy) and adjuvant chemotherapy (6 cycles of doxorubicin (360 mg/m^2) and ifosfamide)	ANED at 7.4 yr
4 (Kolin et al., 2020)	62	6	Biphasic	Yes; incomplete resection due to more extensive disease discovered intraoperatively and PET scan identified metastatic disease.	Positive	Carboplatin and paclitaxel	DOD at 4.6 yr
5 (Kolin et al., 2020)	26	2.1	Biphasic	Yes; two excisions to get negative margins	Negative	External beam radiation (additional details of radiation treatment not available)	DOD at 3.0 yr
6 (Dicken et al., 2010)	33	NA	Biphasic	Yes; radical left hemi-vulvectomy with inguinofemoral lymph node dissection	Close proximity to deep margin (no measurement provided)	Electron beam radiation (total dose of 50 Gy, fractionation not reported) with brachytherapy boost (total dose of 20 Gy)	NR

IMRT, intensity-modulated radiation therapy; ANED, alive with no evidence of disease; DOD, died of disease, NR, not reported.

distant recurrence given the propensity of synovial sarcoma for later recurrence compared to other soft-tissue sarcomas. (Gazendam et al., 2021; Wang et al., 2021) Mean time from diagnosis to local and distant recurrence is 3.6 and 5.7 years respectively. (Gazendam et al., 2021) Additionally, in prior case series of 21 patients with synovial sarcoma, although seven patients developed recurrence within the first 3 years, one patient recurred after 20 years. (Wang et al., 2021).

3.2. *Fertility preservation*

Synovial sarcoma commonly effects young patients, and, in this population, it is especially important to consider toxicities of adjuvant radiation therapy, including effects on fertility. However, only one of the previously described case of vulvar synovial sarcoma (patient 6) specifically discussed fertility outcomes and described successful preservation of fertility.

The effect that radiation has on the potential fertility of the ovary depends on the dose of radiation as well as the patient's age. (Ghadjar et al., 2015) Previous studies support aiming for a mean dose of less than 4 Gy with potential benefit from aiming for even lower doses. (Ghadjar et al., 2015; Chambers et al., 1991; Sudour et al., 2010) Dose to the uterus can also effect fertility outcomes; however, the toxicities associated with radiation are again significantly affected by the age of the patient as the radiosensitivity of the uterus appears to decrease with advancing age. (Ghadjar et al., 2015) Additionally, much of the available data is from the pediatric population, limiting its widespread applicability in adult patients. (Ghadjar et al., 2015; Chambers et al., 1991; Sudour et al., 2010).

For patients who do undergo radiation, there are different options for fertility preservation, including cryopreservation of ovarian tissue that can later be re-implanted post-radiation as well as ovarian transposition, where the ovaries are surgically relocated out of the radiation field. (Ghadjar et al., 2015) Alternatively, the radiation treatment itself can be altered to minimize dosing to critical structures for fertility. In our case we were able to achieve this through careful planning of external beam radiation.

Dicken et al., describe another approach to fertility preservation in their case report (Table 2, patient 6). (Dicken et al., 2010) They used a combination of brachytherapy and electron beam radiation to limit the radiation dose to deeper structures such as ovaries. (Dicken et al., 2010) That patient conceived after completing her treatment with the help of a high-risk obstetrician and reproductive endocrinologist. (Dicken et al., 2010) However, it is important to note that brachytherapy is a more specialized radiation technique that is less widely available than the radiation methods used in our case report.

4. Conclusion

Our report provides a description of a non-invasive approach to delivering adjuvant radiation of the vulva with specific focus on the preservation of fertility. Using an IMRT approach for delivery of radiation allowed for good radiation dosing to the target area with suitably low dose to adjacent organs. Concerns around toxicity with radiation in or near the pelvis can be an important consideration, especially for female patients in their reproductive years. This report adds to the sparse literature on both the management of synovial sarcoma on the vulvar and the use of conformal radiation techniques to preserve fertility in female patients receiving radiation to or near the pelvis.

Patient consent

The patient provided informed consent for their case to be discussed in this case report and submitted to peer reviewed journals.

CRediT authorship contribution statement

Gabriella Schoettle: Conceptualization, Data curation, Resources, Writing – original draft, Writing – review & editing. **Stephanie Gulstene:** Conceptualization, Data curation, Writing – review & editing. **Jason Vickress:** Formal analysis. **Akira Sugimoto:** Data curation. **David D'Souza:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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