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Case report

Unfolding the rarity of SMARCA4 deficient uterine sarcoma (SDUS): A case report

Annie Kanchan Baa [a], Sameer Rastogi [a,*], Sarthak Tripathy [b], Shamim Ahmed Shamim [b], Santosh Menon [c]

[a] Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India
[b] Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India
[c] Department of Pathology, Tata Memorial Hospital, Mumbai, India

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ABSTRACT

Background: SMARCA4 deficient uterine sarcoma (SDUS) is a relatively new entity added to the family of uterine sarcoma characterised by SMARCA4/BRG1 deficiency.
Case: A 62 years old lady presented with abdominal pain and vaginal discharge. On evaluation, found to have a pelvic mass with lymph nodal involvement. She underwent hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy. Preliminary diagnosis made outside was endometrial stromal sarcoma. On further review, had epithelioid and rhabdoid morphology with SMARCA4 loss documented on comprehensive gene profiling. Recurrence within few months of surgery was seen. She was started on gemcitabine and taxol based chemotherapy, showing significant clinical and radiological improvement.
Conclusion: Diagnostic dilemma of this infrequent, aggressive subtype of uterine sarcoma adds to the hindrance in early recognition. Identifying histology surmounted with gene profiling is helpful in establishing diagnosis resulting in early treatment and improving outcomes.

1. Introduction

Uterine sarcomas are extremely uncommon constituting 3–5% of all uterine malignancies (Momeni-Boroujeni and Chiang, 2020). The incidence is 1.5–1.9: 100,000 females per year (Tropé et al., 2012). SDUS (SMARCA4 deficient Uterine sarcoma) is an exceedingly rare and aggressive form of uterine sarcoma which has been recently proposed. It has distinct clinical, pathological and molecular features as compared to other subtype of uterine sarcomas and endometrial cancers. It is typically seen in younger age and has advanced stage at presentation owing to the highly aggressive nature. Vaginal bleeding is the most common symptom with cervical or vaginal masses seen on examination. Morphologically it has rhabdoid features predominantly, hence gained the synonym of "rhabdoid tumour of uterus" too (Kolin et al., 2018).

The biology of SDUS is very similar to small cell carcinoma ovary – hypercalcaemic type (SCCOHT) and SMARCA4 negative thoracic sarcoma. Inactivating SMARCA4 mutations have been regarded as the driving molecular events in the pathogenesis. 6% of SDUS harbour germline mutation. It has also been described as a part of rhabdoid tumour predisposition syndrome (RTPS). The syndrome has an autosomal dominant pattern with an increased predisposition to develop rhabdoid tumours and SCCOHT (Connor et al., 2020).

Retrospective data of less than 25 cases has been published, enumerating clinicopathological details (Kolin et al., 2018; Connor et al., 2020; Kord et al., 2020). However the literature on its management barring surgical expertise in advanced SDUS is still not known. The identification of SMARCA4 mutation has unravelled therapeutic strategies which can combat this obstacle. Preclinical models have demonstrated efficacy of selective EZH2 inhibitors, immunotherapy, CDK4/6 inhibitors; showing promising results (Lin et al., 2019).

Herein we report a patient with advanced SDUS who had excellent clinical and radiological response to chemotherapy. Informed consent was obtained prior to proceedings of the case report.

2. Case discussion

A 62 years old post-menopausal lady, P2L2 with Retinitis Pigmentosa presented with complaints of pain abdomen, vaginal discharge for 2

* Corresponding author.at: Sarcoma Medical Oncology Clinic, AIIMS, New Delhi, India.
E-mail address: samdoc_mamc@yahoo.com (S. Rastogi).

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months duration. She did not report any menstrual irregularities. Her past history was unremarkable and there was no family history of cancer. On evaluation, PET-CT showed a large FDG avid multilobulated soft tissue mass lesion in pelvis, measuring 12.1 × 10.6 × 9.6 cm inseparable from fundus of uterus with para aortic, aortocaval and bilateral external iliac lymph nodes, largest 3.7 × 2.3 cm; with no other sites of metastasis.

The patient underwent surgical intervention outside. Exploratory laparotomy with total abdominal hysterectomy, bilateral salpingo – oophorectomy and infracolic omentectomy with bilateral pelvic lymph node dissection and retroperitoneal lymph node dissection and appendicectomy was done. Post-surgery she developed a large collection in right iliac fossa and lumbar region with multiple air pockets, suggestive of infective collection. She was managed conservatively after the collection was drained out. Post stabilisation, the patient was referred to our centre for further management.

The histopathology examination (Fig. 1) revealed high grade tumour with cell showing epithelioid and rhabdoid morphology. Lymphovascular invasion was seen and the representative pelvic and retroperitoneal lymph nodes were positive for metastasis from uterine sarcoma. On immunohistochemistry, the tumour cells were positive for vimentin, SMA with patchy CD10 and focal cyclin D1. These cells were negative for desmin, caldesmon, ER, LCA, MUM1, MPO, CD30, AE1/AE3, c-kit and HMB-45. Ki 67 was 50–60% and INI1 protein was retained. FISH analysis was done to further subtype the uterine sarcoma.

In view of YWHAE FISH negativity, this was not a YWHAE translocated endometrial stromal sarcoma. Overall features favoured an undifferentiated uterine sarcoma with stage IIIC. In view of the rhabdoid morphology, a SMARCA4 deficient undifferentiated uterine sarcoma was kept as a likely possibility. We did comprehensive genomic profiling by Foundation One heme. This assay utilized DNA sequencing to interrogate 406 genes as well as selected introns of 31 genes involved in rearrangements, in addition to RNA sequencing of 265 genes. It clinched our diagnosis of SDUS, showing SMARCA4 loss. This was a copy number alteration; total count for this gene being zero. The RAD 21 and AKT3 amplification were additionally seen along with stable microsatellite status and low tumour mutation burden. PDL1 was also reported as negative. The sequencing yielded negative results for PTEN, PIK3CA, TP53 and CTNNB1.

She was started on tb. pazopanib 400 mg once a day as her performance status was borderline and tolerance to cytotoxic therapy was questionable. However after one month she presented with complaints of abdominal pain and vomiting. X-ray abdomen was done which revealed multiple dilated small bowel loops with air fluid levels suggestive of small bowel obstruction. Ultrasonography revealed right iliac fossa mass measuring 8.7 cm × 7.1 cm × 5.4 cm along with deposits in mesentery and peritoneum along surface of small bowel causing minimal dilation of proximal bowel loops. PET-CT was suggestive of a pelvic mass (Fig. 2). She was managed symptomatically, with ryle's tube drainage, intravenous fluids and other supportive care. Our patient was then started on gemcitabine (800 mg/m^2) and nab-paclitaxel (120 mg/m^2) based chemotherapy every three weeks. She tolerated it well, and showed significant clinical response with resolution of symptoms of obstruction. Post three cycles, she had excellent response both clinically and radiologically. Repeat PET-CT (Fig. 3) was suggestive of partial response based on RECIST 1.1 criteria. She was continued on the same regimen, and reassessment was planned after six cycles.

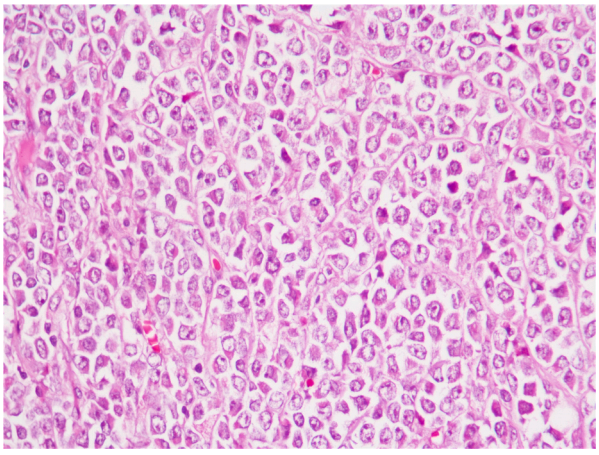


Fig. 1. The photomicrograph shows a cellular sarcomatous tumour with discrete epithelioid to rhabdoid appearing cells which have vesicular nuclei and prominent nucleoli. Interspersed thin walled capillary sized vessels are seen. (H & E; Magnification × 200).

3. Discussion

The SMARCA4 gene is located on chromosome 19p and is part of the SWI/SNF (mating type Switching defective/Sucrose Non Fermenting) chromatin-remodelling complex. SMARCA4 protein also known as BRG1 protein is a transcription activator which is ATP dependent.

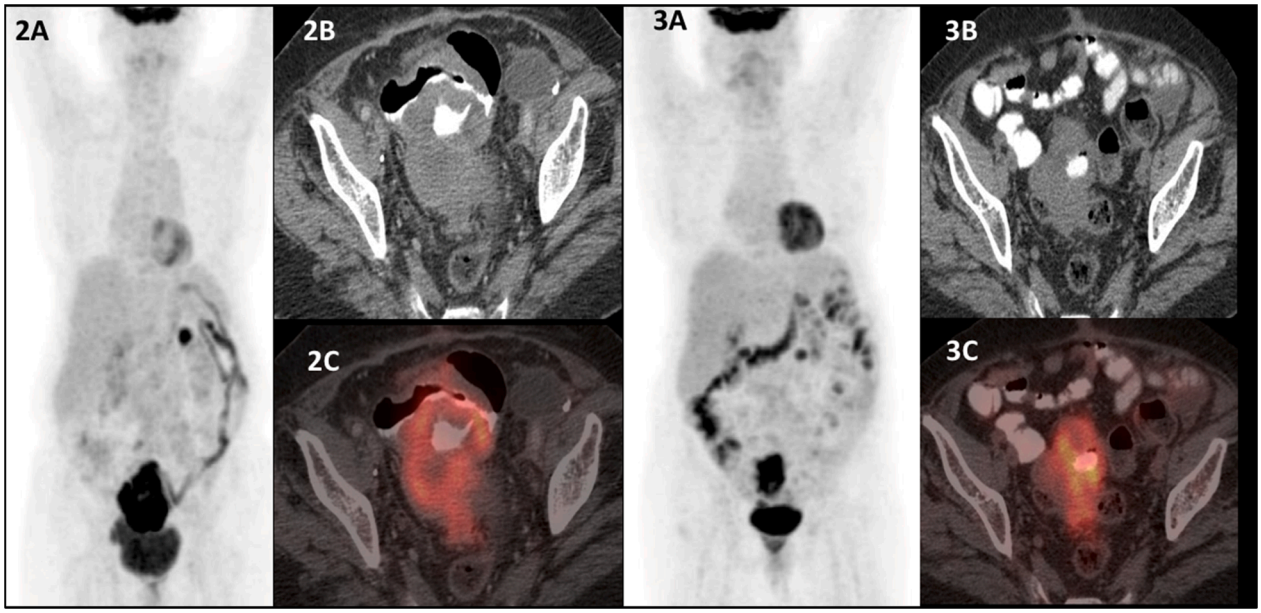
SMARCA4 has been considered as a tumour suppressor gene but both loss of protein expression and upregulation has been associated with malignancy (Muppala et al., 2017). The unearthing of SMARCA4 mutation in uterine sarcoma has led to a new variant with unique, aggressive clinicopathologic and molecular features.

Our patient presented at a higher end of the age spectrum as compared to literature. In a case series by Kolin et al. (2018) the median age was 33 years and Lin et al. (2019) reported a median 49 years. However till now oldest patient reported is 72 years. Our patient presented initially with abdominal pain which is a lesser common presentation, but she was at an advanced stage (IIIc) at baseline. Patients commonly present as vaginal bleeding as the predominant symptom along with cervical and vaginal masses. In a study by Lin et al. (2019) only 19 percent of patients presented with stage I or II implicating aggressive nature of this tumour. They had lymph nodes involvement, high grade and lymphovascular invasion paralleling the features seen in our patient. Lin et al. (2019) also demonstrated 30% lymph nodal involvement and 100% lymphovascular invasion, however the data of this cohort is small to comment upon for SDUS causing lympahdenopathy.

Our patient had large cells arranged in sheets and lobules with areas of geographical necrosis, abundant eosinophilic cytoplasm and pleomorphic nuclei with irregular nuclear membranes, vesicular chromatin and prominent nucleoli. Lin et al. (2019) and Kolin et al. (2018) describe similar morphology in SDUS having diffuse sheets of rhabdoid or large cells along with epithelioid cells with high grade nuclear atypia, and hence the name "rhabdoid tumour of uterus" (Kolin et al., 2018). Leaf like architecture ("phyllode") with stromal hyalinization have also been described. However few cases have been also reported with small and spindle cell variant having minimal nested pattern WT1 is generally negative, while CD10 and Cyclin D1 is patchy or negative (Lin et al., 2019).

Undifferentiated/dedifferentiated carcinoma, small cell carcinoma of the ovary hypercalcaemic type, high grade endometrial stromal sarcoma, adenosarcoma are the common differential diagnosis that come across while dealing with SDUS causing diagnostic dilemmas. SCCOHT has similar clinicopathologic features (young age, aggressive nature, morphology, loss of SMARCA4 expression) but have salient points of distinction. Clinical presentation depends on the site of origin: SDUS arises from uterus and may have bilateral adnexal involvement; being WT1 negative. SCCOHT generally present with abdominal distension with unilateral adnexal involvement rather than vaginal bleeding and cervical mass (Kolin et al., 2018). Hence identifying histology, tumour burden, judiciously using immunohistochemistry and molecular analysis can help in differentiation as was evident in our patient.

Comprehensive genomic profiling of the patient yielded SMARCA4 loss along with RAD21 and AKT3 amplification. This played a vital role



Figs. 2 and 3. (At baseline presentation): 2A – Maximum intensity projection image of FDG PET-CT showing increased tracer uptake in the pelvic region corresponding to large pelvic mass (measuring 7.5 × 5.5 cm) on axial CT section (2B) showing FDG uptake in the fused PET-CT image (2C). (Post 3 cycles of chemotherapy): 3A – Maximum intensity projection image of FDG PET-CT showing increased tracer uptake in the pelvic region corresponding to large pelvic mass on axial CT section (3B) showing FDG uptake in the fused PET-CT image (3C). As compared to previous PET-CT there is reduction in size of the pelvic mass (measuring 4 × 3.5 cm) suggestive of partial response to therapy.

in establishing the diagnosis. In the study by Lin et al. (2019), frameshift and nonsense mutations were commonly seen with SMARCA4 loss. Also alterations apart from SMARCA 4 were found in 19% of cases (3 out of 16). 13% had P53, 6% had RB1 and CTNNB. 81% were microsatellite stable along with a low mutation burden (mean 1.7mut/Mb). In our case RAD and AKT were unique, while microsatellite stability and TMB status corresponded to seen in previous studies. We did not do SMARCA 4 germline testing, as patient is on treatment and is in higher age spectrum. However it is pertinent to get germline mutation done as heterozygous germline mutations in *SMARCA4* can be been associated with rhabdoid tumour predisposition syndrome (Connor et al., 2020). Counselling of our patient's children was done to get germline testing, unfortunately it was declined.

Our patient had rapid progression post-surgery similar to documented aggressive clinical course in literature. Based on preliminary histopathology report, pazopanib was started based on EPAZ trial (Grünwald et al., 2020) which had showed non inferior results in terms of progression free-survival (HR:1.00, 95% CI: 0.65–1.53) when compared to anthracyclines. Decreased myelotoxicity, and comparable overall response rates were seen (12.3% vs 15.4%) with pazopanib. The patient however progressed on pazopanib after one month. Data on effective chemotherapy with response rates in SDUS is sparse. There is only case report by Kord et al. (2020) in which chemotherapy (gemcitabine + docetaxel) use has been documented however RECIST 1.1 response evaluation is lacking. Our patient had excellent response to gemcitabine/nab paclitaxel.

The median survival reported post aggressive surgery is 9 months in Kolin et al. (2020), while 7 months with range varying from 1 to 43 months is reported in earlier study by Kolin et al. (2018). This emphasizes the fatality of the disease, reinforcing the need for early recognition and treatment.

However despite the aggressive nature and no certain treatment modality instrumental in improving survival, SMARCA4 mutation identification has therapeutic implications. There are preclinical models demonstrating benefit and have opened up a new dimension for therapy in SDUS (Chan-Penebre et al., 2017). Selective EZH2 inhibitors like Tazemetostat is in phase II trial having antiproliferative and antitumor effects and is being evaluated in recurrent endometrial and ovarian carcinoma(NCT 03348631). Immunotherapy has also shown benefit despite having a low tumour mutational burden in SCCOHT, suggesting extrapolation in SDUS owing to the similar biology (Jelinic et al., 2018). CDK4/6 inhibitors (palbociclib/abemaciclib) are another potential targeted therapies which need further studies to demonstrate effectiveness in SDUS.

CRediT authorship contribution statement

Annie Kanchan Baa: Writing - original draft, review & editing. **Sameer Rastogi:** Conceptualization, Resources, Supervision. **Sarthak Tripathy:** Investigation. **Shamim Ahmed Shamim:** Supervision. **Santosh Menon:** Investigation.

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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