

# Uterine tumor resembling ovarian sex cord tumor: A series of six cases displaying varied histopathological patterns and clinical profiles

Kavneet Kaur, Madhu Rajeshwari, Niteeka Gurung, Hemanth Kumar, Mehar C. Sharma, Rajni Yadav, Sunesh Kumar<sup>1</sup>, Smita Manchanda<sup>2</sup>, Seema Singhal<sup>1</sup>, Sandeep R. Mathur

Departments of Pathology, <sup>1</sup>Obstetrics and Gynaecology and <sup>2</sup>Radiology, All India Institute of Medical Sciences, New Delhi, India

## Address for correspondence:

Prof. Sandeep R. Mathur, Department of Pathology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India.  
E-mail: [mathuraiims@gmail.com](mailto:mathuraiims@gmail.com)


## ABSTRACT

**Introduction:** Uterine tumors resembling ovarian sex cord tumor (UTROSCT) are a unique group of neoplasms with diverse morphology and immunophenotypic characteristics, coexpressing sex cord, epithelial, and smooth-muscle markers. To date, less than 100 cases have been reported and there is paucity of data concerning their clinical behavior. **Materials and Methods:** All cases of uterine body tumors diagnosed over a period of two and a half years (2016-2018) were retrieved. Histopathological features were reviewed and extended panel of immunohistochemistry was performed to identify cases of UTROSCTs. **Results:** Six cases of UTROSCTs were identified with a median age of 46.5 years. Four of them presented with menorrhagia, while two with postmenopausal bleeding including one with a history of carcinoma breast. Three of these cases were initially misdiagnosed as endometrial stromal sarcoma and adenocarcinomas. They all underwent hysterectomy with bilateral salpingo-oophorectomy. **Conclusion:** It is considered a tumor with low malignant potential; however, one out of six cases (16.7%) in our study showed metastasis, within 1 year of diagnosis. It is important to recognize this entity as it mimics a wide range of both benign and malignant tumors. Molecular pathogenesis and exact management protocols remain elusive due to rarity, hence, multi-institutional studies are warranted.

**KEY WORDS:** Mesenchymal neoplasm, ovarian, sex cord stromal, uterus

## INTRODUCTION

Uterine tumor resembling ovarian sex cord tumor (UTROSCT) is a rare tumor with uncertain histogenesis. World Health Organization (WHO) classification of tumors of female reproductive organs, 2014 defines it as a “neoplasm that resembles ovarian sex cord tumors, without a component of recognizable endometrial stroma.”<sup>[1]</sup> To date, less than 100 cases have been reported in literature.<sup>[2-15]</sup> These tumors are intriguing as they have a polyphenotypic immunohistochemical expression profile showing positivity with sex cord, smooth muscle, and epithelial markers along with hormone receptors.<sup>[16,17]</sup> They most commonly present in the middle age (perimenopausal or menopausal women) with abnormal uterine bleeding and hence have been treated by hysterectomy. There is limited data in literature concerning the behavior and clinical profile of UTROSCTs. They appear to have a low malignant potential. However, there have been cases with recurrence and even metastasis to remote sites.<sup>[9-14]</sup> Few cases presenting in reproductive age group have been treated by fertility preserving conservative surgery.<sup>[5-7]</sup> It is a histomorphological diagnosis as there are no imaging characteristics of the tumor. Hence, a high index of suspicion along with a panel of

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DOI: 10.4103/IJPM.IJPM_340_19
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immunohistochemical markers is needed to rule out the differentials and arrive at the correct diagnosis. Here, we present six cases of UTROSCT, diagnosed in the Department of Pathology, AIIMS.

## MATERIALS AND METHODS

All cases of uterine body tumors diagnosed over a period of 2 and a half years (2016–2018) were retrieved. Histopathological features were reviewed

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**How to cite this article:** Kaur K, Rajeshwari M, Gurung N, Kumar H, Sharma MC, Yadav R, *et al.* Uterine tumor resembling ovarian sex cord tumor: A series of six cases displaying varied histopathological patterns and clinical profiles. *Indian J Pathol Microbiol* 2020;63(Special):S81-6

by three pathologists (KK, MC & SM) to identify cases of UTROSCTs. Extended panel of immunohistochemistry (IHC) was performed to establish diagnosis, which included sex cord stromal markers: Calretinin (1:100), MIC2 (CD99) (1:200; Spring Biosciences, CA, USA), Inhibin (1:150, Biocare Medical, CA, USA); epithelial markers: Epithelial membrane antigen (1:1000; Dako, Denmark), cytokeratin (CK) (1:1000), CK7 (1:1000) (Scytek, YT, USA), CK20 (1:200) (BioSB, CA, USA); mesenchymal markers: Vimentin (1:200), smooth muscle actin (1:200; Spring Biosciences, CA, USA), Desmin (1:100, Scytek, YT, USA); hormonal receptors: Estrogen receptor (ER), progesterone receptor (PR) (1:400) (Spring Biosciences, CA, USA); WT1 (1:200; Cell Marque, Germany); cyclin D1 (1:100, Spring Biosciences, CA, USA), CD10 (1:50) (for endometrial stromal sarcoma); myogenin (1:200) (for rhabdomyosarcoma); melan A (1:500) (for Perivascular epithelioid cell neoplasms (PEComa)) (BioSB, CA, USA); CD34 (1:200; Spring Biosciences, CA, USA), CD31 (1:50; Spring Biosciences, CA, USA) (for vasoformative tumors); MIB1 (Ki-67) (1:200, Spring Biosciences, CA, USA).

## RESULTS

A total of 530 uterine body mesenchymal tumors were diagnosed over the study period. Most common were leiomyomas (88.2%). Endometrial stromal sarcomas (both high-grade and low-grade) constituted 4.2%. A total of six cases of UTROSCT were identified constituting 1.1% of mesenchymal tumors of uterine body. Clinical and pathological findings [Table 1] of all the six cases are summarized below.

### Clinical findings

All patients presented in their 5<sup>th</sup> decade (age range: 42–50 years) with the median age of 46.5 years. Four of them presented with menorrhagia, while two with postmenopausal bleeding, with symptom duration ranging from 15 days to 5 years. One of the patients (Case 4) had a history of carcinoma breast (NST, ER, and PR positive, Her-2/neu negative; pT2N0M0) diagnosed 3 years back, for which, she had undergone wide local excision with sentinel lymph node biopsy. Following which, she received 15 cycles of radiotherapy

**Table 1: Summary of clinical and pathological details of all patients with UTROSCT**

	Age	Signs and symptoms	Size	Imaging	Surgery	Histopathological features	IHC				Adjuvant therapy	Follow up	Duration
							Sex-cord stromal	Epithelial	Mesenchymal	Hormonal receptors			
Case 1	49	Bleeding per vaginum x 1.5 months	7.5 cm	An echogenic lesion without vascularity in the lower uterine segment	Type III radical hysterectomy with BSO	Tumor cells arranged in plexiform cords, tubules and nests in myxoid stroma	MIC2 + Calretinin -	CK focal + EMA focal + CK7-CK20-	Vimentin + SMA focal + Desmin -	ER+PR focal +	None	NED	2 years
Case 2	42	Menorrhagia x 5 years	6.2 cm	Hypoechoic lesion in the anterior wall of uterus	TAH with BSO	Cellular tumor with polygonal cells in nests and sheets	Calretinin + MIC2focal + Inhibin - WT1 -	CK focal +	Vimentin + SMA focal + Desmin - Myogenin-	ER focal+PR focal +	None	NED	1 year 6 months
Case 3	47	Menorrhagia and anemia x 2 years	9.3 cm	Ill-defined lesion in the body of the uterus	TAH with BSO	Oval to fusiform cells arranged in plexiform cords, nests, sheets in myxoid stroma	Calretinin + Inhibin -	CK -	Desmin + SMA -Myogenin -	ER+PR +	6 cycles of paclitaxel and carboplatin	Recurrence and metastasis	7 months
Case 4	43	Post menopausal bleeding x 15 days	1.0 cm	No mass lesion	TAH with BSO	Small round to oval cells arranged in cords and lobules separated by smooth muscle bundles	Calretinin + Inhibin -	CK -	Vimentin + SMA+Desmin -	ER+PR +	None	NED	1 year
Case 5	46	Menorrhagia x 2 years	4.0 cm	Bulky uterus two large fibroids in fundus	TAH with BSO	Nests, retiform tubules and trabeculae separated by hyalinized stroma	Calretinin + Inhibin -	CK -	Desmin + SMA+	ER+PR +	None	NED	4 weeks
Case 6	50	Post menopausal bleeding	NA	Fibroid	TAH with BSO	Sheets, cords and perivascular arrangement around hyalinized blood vessels	Calretinin +	CK +	Desmin + SMA -	ER+PR +	None	NA	NA

TAH with BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy; CK: Cytokeratin; EMA: Epithelial membrane antigen; SMA: Smooth muscle actin; ER: Estrogen receptor; NED: No evidence of disease

and 8 cycles of chemotherapy, and was put on tamoxifen for a period of 5 years.

Ultrasonography revealed mass lesions in five cases, except case number 4. The size of the tumors ranged from 1 cm (not detected by ultrasound) to 9.3 cm and was located variably in fundus, uterine body and lower uterine segment. In three cases (cases 2, 4, and 5), a diagnosis of bulky uterus with fibroids was given. Magnetic resonance imaging (MRI) of case 1 confirmed the presence of a lobulated hyperintense tumor measuring  $7.2 \times 6.5 \times 7.5$  cm with the possible radiological diagnosis of endometrial carcinoma. MRI of case 2 revealed a mass in the anterior wall of uterus measuring  $6.2 \times 5.6$  cm, suggestive of fibroid. None of the other patients underwent MRI.

All patients were subjected to hysterectomy and bilateral salpingo-oophorectomy.

### Pathological examination

Endometrial aspirate (EA) was performed for cases 1, 3, and 5. EA of case 1 was fragmented and showed mucoid material along with atypical cells and hence a possibility of mucinous adenocarcinoma was given. EA of cases 3 and 5 did not reveal any tumor and showed inactive tubular endometrial glands and secretory endometrium, respectively. Three cases, case numbers 2, 3, and 6, who were operated at an outside hospital first, an initial diagnosis of low-grade endometrial stromal sarcoma, a mesenchymal neoplasm showing extensive myxoid change with tumor infiltrating into myometrium and into cervical stroma and a tumor possibly an adenocarcinoma was rendered at their respective pathology (outside) laboratories, before review of slides at our institute.

### Gross

Case 1 showed a grayish circumscribed tumor with areas of hemorrhage in the isthmic portion with extension into cervical stroma. Serial slicing of the uterus of Case 4 revealed small yellowish nodules (three in number) ranging in size from 0.8 to 1 cm. A polypoid mass measuring 4 cm with gray-white nodular cut surface was identified in the endometrial cavity of the uterus of case 5. Three cases (Cases 2, 3, and 6) were operated at an outside hospital and we only received slides and blocks from the tumor for review. Bilateral ovaries and fallopian tubes were within normal histological limits for age in all the cases.

### Histopathology and immunohistochemistry

On microscopic examination [Figure 1] of the hysterectomy specimens (Cases 1, 2, and 5), the tumors had pushing margins, and were fairly to well circumscribed. The tumor of Case 3 had infiltrative edges into the myometrium. The tumor in cases 4 and 6 had pseudoinfiltrative edges, with incorporated smooth muscle bundles.

The tumor cells were arranged most commonly in plexiform cords, nests, and trabeculae. Three of the cases showed tumor in sheets as well (cases 2, 3, and 5). Two cases (cases 2, 5) along with

cords and nests also showed presence of retiform tubules. Case 6 had focal perivascular arrangement. The tumor cells were small, round to oval with scant cytoplasm, hyperchromatic nuclei in four cases. However, two cases showed polygonal epithelioid cells with moderate amount of cytoplasm (cases 2 and 6), and vesicular nuclei with conspicuous nucleoli and occasional nuclear grooves. Fusiform to spindle-shaped cells were identified in cases 1 and 3. In tumors of three cases, the tumor cells were embedded in an abundant myxoid stroma (cases 1, 3, and 4); however, in one of the tumors, there was hyalinized stroma (cases 5, 6). All cases showed minimal nuclear pleomorphism. Necrosis was not seen in any of the cases. Mitosis of 1-3/10 hpf was identified. MIB1 labeling index ranged from 2 to 3%.

On immunohistochemistry, all cases showed either MIC2 or calretinin positivity with variable positivity for WT 1 and inhibin. Three of the cases were immunopositive for cytokeratin. Among markers for mesenchymal differentiation, all cases showed either vimentin or desmin positivity. Four of them also showed focal smooth muscle actin positivity. Immunohistochemistry for hormonal (estrogen and progesterone) receptors was positive in all cases. All the tumors were negative for CD10 ruling out low-grade endometrial stromal sarcoma. Also, CD56, melan A, cyclin D1 done in few cases for differential diagnosis of neuroendocrine tumor, melanoma, and high-grade endometrial stromal sarcoma, were negative. Many tumors ranging from benign to malignant fall in the differential diagnosis of this tumor [Table 2].

### Prognosis

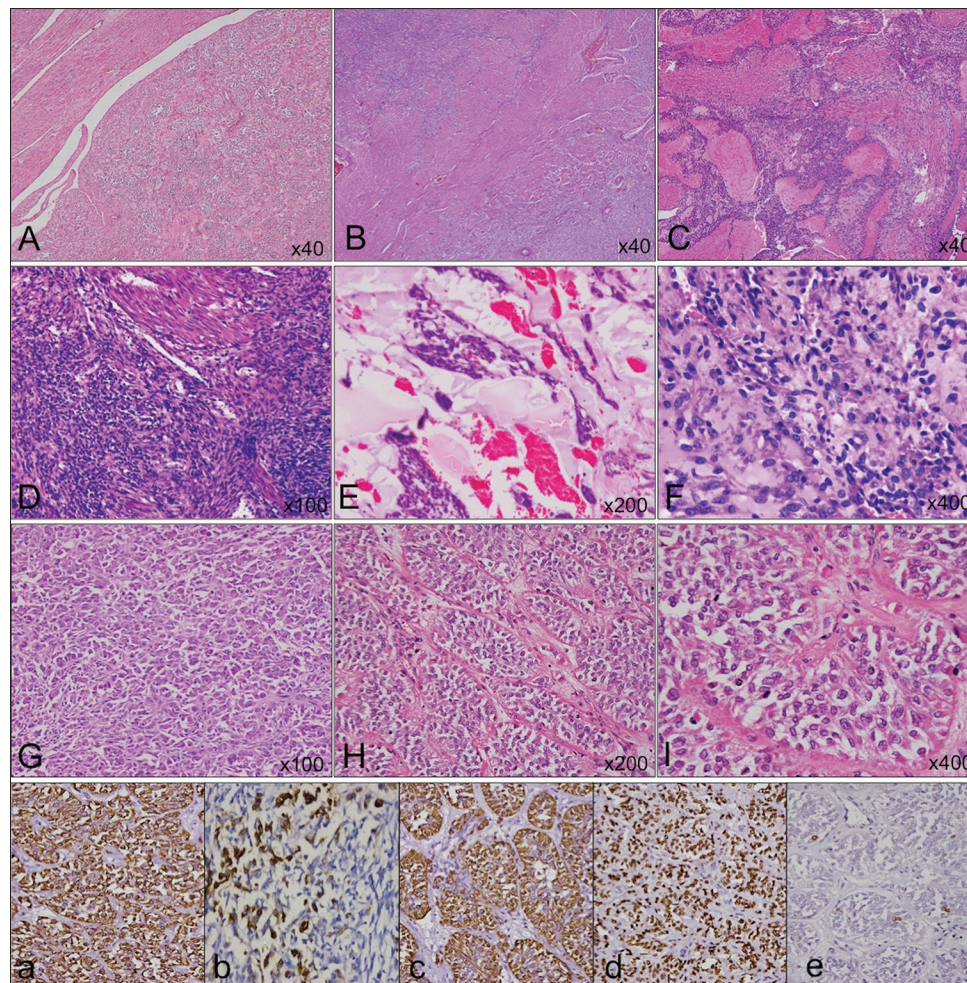
All cases except, case 3, only underwent surgery, with no adjuvant therapy and have no evidence of disease at follow up period ranging from 4 weeks to 2 years. However, case 3 presented with bleeding per vaginum 7 months post the initial surgery. MRI pelvis revealed a large multiseptated lesion containing blood fluid levels in pelvis, suggestive of recurrent disease. Positron emission tomography - computed tomography (PET-CT) scan showed posthysterectomy status, multiple large faintly fluorodeoxyglucose (FDG) avid pelvic deposits, and enlarged retroperitoneal lymph nodes and multiple noncalcified bilateral lung nodules, suggestive of metastasis. She was given six cycles of paclitaxel and carboplatin-based chemotherapy. Her disease is stable now.

The details of all cases have been summarized in Table 1.

### DISCUSSION

Morehead and Bowman initially described a peculiar case which they called uterine neoplasm resembling a granulosa cell tumor.<sup>[2]</sup> In 1976, Clement and Scully clarified the concept of sex cord differentiation in uterine tumors and categorized them into two groups: Group I: Endometrial stromal tumors with <50% foci of sex cord differentiation, and Group II: Composed predominantly or exclusively (>50%) of sex cord-like elements classified as UTROSCTs.<sup>[3]</sup> However, WHO 2014 catalogues UTROSCTs under endometrial stromal and related tumors with no endometrial stromal component.<sup>[1]</sup>





**Figure 1: Histomorphology A-I (Hematoxylin & Eosin):** Low power magnification (a-c) of different cases showing a well demarcated tumor from the myometrium (Case 5) (a); a tumor with pseudoinfiltrative pattern (Case 4) (b); and a tumor with infiltration into smooth muscle bundles (Case 3) (c). Different architectural patterns and morphology of UTROSCT identified: Small tumor cells with scant cytoplasm arranged in sheets and nests (Case 3) (d), small oval cells in nests embedded in a myxoid matrix (Case 1) (e); Tumor cells in sheets in a hyalinized stroma (Case 5) (f); Epithelioid tumor cells in sheets and vague tubules (Case 2) (g); Tumor cells arranged in nests, hollow, and solid tubules (Case 6) (h), having moderate eosinophilic cytoplasm with eccentric nuclei (i) Immunohistochemistry (a-e): Tumor cells immunopositive for calretinin (a), cytokeratin (b), desmin (c), estrogen receptor (d) with a low MIB-1 labeling index (e)

These tumors are most commonly seen in perimenopausal or menopausal women (mean age 51), although can occur over a wide age range (22–84 years). Patients present most frequently with abnormal uterine bleeding (AUB). They are commonly myometrial tumors, followed by submucosal location. Our cases were all in the middle-aged group and presented with AUB. There are no definitive imaging characteristics of the tumor. It can mimic leiomyomas when myometrial and circumscribed; leiomyosarcoma when myometrial along with hemorrhage and irregular borders; and even endometrial carcinoma when submucosal in location. Not only there are challenges to diagnose this tumor on imaging, endometrial aspirates/biopsies can sometimes be wrongly diagnosed,<sup>[15]</sup> as was the case in three of our cases.

UTROSCTs are a unique group of uterine neoplasms with diverse morphology and immunophenotypic characteristics, coexpressing sex cord, epithelial, and smooth-muscle markers.<sup>[16,17]</sup> They show

a wide spectrum of morphological features leading to wide differential diagnoses [Table 2]. UTROSCT resembles the sex cord tumors in ovary; however, it does not reiterate any of the specific category of ovarian sex cord stromal tumor. Histomorphology can range from spindle-shaped, oval to epithelioid cells with scant to abundant cytoplasm arranged in an assortment of architectural patterns ranging from diffuse sheets, nests, cords, trabeculae, rarely retiform, or glomeruloid pattern or tubules and may be embedded in a mucoid/myxoid stroma. Sometimes there can be clearing of cells and even luteinization of stroma. Generally, it is a well-circumscribed tumor, however, it can appear to infiltrate into adjacent myometrium due to incorporated smooth muscle bundles. Hence, it can mimic a myriad of benign and malignant neoplasms including epithelioid leiomyoma, well-differentiated endometrioid carcinoma and endometrial stromal sarcoma with sex cord-like differentiation [Table 2]. Necrosis, mitosis (>2/10 hpf), and nuclear pleomorphism, vascular invasion are usually not present; however, their presence

**Table 2: Differential diagnosis of UTROSCTs with a highlight on clinical, pathological, and molecular genetic differences between different entities**

Differential diagnosis	Mean age (years)	Histology	Sex-cord markers Calretinin, MIC2, Melan A, CD56, FOX L2, SF1	Epithelial markers CK, EMA, CAM5.2	Mesenchymal markers SMA, Desmin, SMMHC	WT1	Molecular profile	Management	Prognosis/ behavior
UTROSCT	51	Well circumscribed Bland cytological features Sheets, cords, nests, trabeculae, retiform	+	+	+	+	Amplification on chromosome 17q11.2, SUZ12 gene	Conservative	Good Low malignant potential
Low grade Endometrial stromal sarcoma (LG-ESS)	52	Tongue-like invasion into myometrium Sheets showing smooth muscle, sex cord-like differentiation or endometrioid-like glands	-	- CK+/-	- Desmin -/+	+	t (7;17) JAZF1 and SUZ12 (JJAZ1) fusion	Radical Hysterectomy	Poor Malignant
Epithelioid leiomyoma	30	Well circumscribed Polygonal cells in sheets, cord and trabeculae	-	-	+	-	Rearrangements of HMGA locus t (12;14) q15;q23	Conservative	Good Benign
Endometrioid carcinoma	59	Glandular or villoglandular with branching and complex architecture	-	+	-	-	Mutation of PTEN, PIK3CA, KRAS, TP53	Radical Hysterectomy	Poor Malignant
PEComa	51	Well circumscribed or infiltrative margins Epithelioid and spindle cells in diffuse sheets and fascicles	- Except Melan A	-	-	-	LOH of TSC2 TFE3 gene rearrangement	Simple Hysterectomy	Intermediate Uncertain malignant potential
Metastasis from ovary of sex-cord stromal tumors	36	Dispersed or nodular aggregates Annular tubules, nests, solid, cysts	+	-	-	+	Germline mutation of STK11	Surgical	Not known

has been linked to an aggressive behavior.<sup>[10]</sup> However, the case in our study which showed metastasis, did not have necrosis or increased mitosis, but it did have more infiltrative borders.

Although UTROSCTs are considered benign neoplasms or neoplasms with uncertain malignant potential, there is limited data in literature regarding their behavior. One out of our six cases showed recurrence along with distant metastasis within 1 year of diagnosis. Among the published cases, Moore and McCluggage documented metastasis in 8 out of 34 cases.<sup>[10]</sup> Previously, there are four cases published in literature, which showed metastasis.<sup>[9,11-13]</sup> This definitely paints a more malignant potential of these tumors. Hence, it is important to look for histopathological and molecular characteristics of this subset of aggressive tumors. Moreover, the number of such cases is too less to derive any logical conclusions. However, none of the studies have delineated any molecular characteristics which differentiate the aggressive from more benign subset of these rare and enigmatic tumors.

Molecular pathogenesis remains elusive due to rarity. One case has been found to harbor t(X;6)(p22.3;q23.1) and t(4;18)(q21.1;q21.3) and another tumor was found to have focal amplification on chromosome 17q11.2 including SUZ12 gene.<sup>[18]</sup> The molecular signature of endometrial stromal sarcomas (JAZF1/SUZ12) fusions were not found in UTROSCTs.<sup>[19]</sup>

Management strategies are not well defined because of rarity and also because of varied clinical course and occurrence over a wide age range. Surgery, i.e., hysterectomy with or without

salpingo-oophorectomy has been considered the treatment of choice. However, when the tumor occurs in reproductive age group, some authors have proposed a fertility preserving conservative surgical management.<sup>[5-7]</sup>

Role of adjuvant chemotherapy remains unclear and has only been recommended in cases with recurrence or metastasis. Some authors have proposed the use of bleomycin, etoposide, and cisplatin in such cases.<sup>[14]</sup> Treatment with hormonal receptor antagonists/ modulators has been considered, though its utility is not well known.<sup>[20]</sup> However, due to single case reports, there are no set guidelines for treatment of such cases and the clinicians have to resort to similar treatment protocols as used for endometrial stromal sarcomas in cases of recurrence/metastasis.

It is important to recognize this entity and differentiate it from other benign as well as more aggressive lesions, to define its behavior and treat the patients accordingly. Select immunostains may be helpful but are not required; however, familiarity with the morphologic features of these and other mesenchymal neoplasms is crucial. They are extremely rare enigmatic tumors whose incidence, management protocols, and molecular histogenesis remain unclear. Hence, multiinstitutional studies are warranted.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest. Compliance with ethical standards.

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