CASE REPORT

Cellular leiomyoma versus endometrial stromal tumor: A pathologists' dilemma

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ABSTRACT

Uterine smooth muscle tumors and endometrial stromal tumors (ESTs) are the two major types of mesenchymal tumors of the uterus, the latter being fairly uncommon. Among these, endometrial stromal sarcoma (ESS) accounts for 0.2-1.5% of all uterine malignancies. Although routine histopathological examination is sufficient to distinguish between ESS and smooth muscle tumors in most of the cases, the distinction between ESTs and highly cellular leiomyomas (CMs), on several occasions becomes a great diagnostic challenge for the pathologist. The differentiation between EST and CM is necessary on account of the variable clinical course and slight variation in the therapy. However, this is difficult due to the tendency of endometrial stromal cells to differentiate into well-developed smooth muscle cells as well as overlapping immunohistochemical profile in some cases. We hereby report a series of cases which posed a diagnostic challenge to us as to whether they are CMs or ESTs. We therefore discuss the histological features which helped us resolve this dilemma as well as the utility of immunohistochemistry (IHC) as a diagnostic aid in arriving at a final diagnosis in such problematic cases.

Key Words: Cellular leiomyoma, endometrial stromal sarcoma, endometrial stromal tumor

INTRODUCTION

Endometrial stromal tumors (ESTs) are among the least common neoplasms of the uterus. Among these, endometrial stromal sarcoma (ESS) accounts for 0.2-1.5% of all uterine malignancies.[1] ESTs closely recapitulate stroma seen in proliferative endometrium. Low-grade ESS (LGESS) can sometimes overlap diagnostically with cellular leiomyoma (CM),especially when prominent smooth muscle or fibroblastic differentiation is present.[2] This becomes important in the light of limited experience with EST as these are rare tumors with limited case series in the literature.[3-8] The role of immunohistochemistry (IHC) has also been evaluated by several authors[6-8] in this regard, with few markers like CD-10 and caldesmon emerging as useful adjuncts in differentiating between ESTs and CMs.

We hereby report a series of cases which posed a diagnostic challenge to us: CM versus EST. We therefore discuss the histological features which helped us resolve this dilemma as well as the utility of IHCas a diagnostic aid in arriving at a final diagnosis in such unconfirmed cases.

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CASE REPORT

Case 1

A 46-year-old female presented with menorrhagia and dull abdominal pain. Ultrasonography revealed a well-circumscribed mass, 4.8 × 4.6 cm, suggestive of a leiomyoma. Abdominal hysterectomy was performed without salpingo-oophorectomy. Uterus showed a well-circumscribed intramural mass measuring 5 × 2 cm with a homogenous, yellowish white cut surface. Microscopically, tumor was well-delineated comprising of uniform small round nuclei with granular chromatin [Figure 1]. A differential diagnosis of endometrial stromal nodule (ESN) and leiomyoma was considered. On further sampling, focal areas of epithelioid-like structure reminiscent of sex cord differentiation were also seen. Moreover, IHC for CD 10

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was positive, while desmin staining was negative. So, the final diagnosis of ESN was rendered. This case has been published as a case report.[9]

Case 2

A 39-year-old female presented with irregular bleeding per vaginum and acute retention of urine. Per speculum examination revealed a large shaggy mass protruding from cervical os. Ultrasonography was suggestive of a leiomyomatous polypmeasuring 9 × 8 × 8 cm. Polypectomy was performed. Cutsurface of the polyp was fleshy, grayish pink in color. Microscopic examination revealed a cellular tumor comprising of round to spindle-shaped uniform appearing cells with oval nuclei [Figure 2]. Mitosis was less than 3/10 hpf. Myometrial invasion could not be commented upon as stromal myometrial interface was not included in the polypectomy specimen. Differential diagnosis included EST (ESN/LGESS) and CM. Patient underwent a hysterectomy with bilateral salpingo-oophorectomy. A polyp was seen in the posterior wall of uterus. Microscopy revealed similar findings. Tumor cells were arranged concentrically around spiral arteriole-like vessels with cord like projections into myometrium. On IHC, tumor cells were positive for CD 10, negative for desmin, thereby ruling out a CM. Moreover, focal areas with sex cord like differentiation showed inhibin reactivity. Hence, a final diagnosis of LGESS with sex cord differentiation was given. This case was published as a case report.[10]

Case 3

A 40-year-old female presented with irregular heavy bleeding per vaginum continuously since the last 2 months. Per speculum examination revealed a large polypoidal mass projecting from the os with anterior cervical lip erosion. Ultrasonography was suggestive of a cervical fibroid, 4.3 × 3.9 cm. Polypectomy was performed with removal of the mass in labia majora. Grossly, a polyp measuring 6 × 5 × 5 cm was received with a firm, whitish yellow cut surface. Microscopically, sections showed a tumor composed of plump to spindle cells with moderate cytoplasm with round to oval nuclei. Tumor cells were arranged in fascicles at places with many entrapped normal endometrial glands [Figure 3]. Focally, the tumor cells were seen to form a circumferential whorled pattern around these glands. Mitosis was 1-2/10 hpf. Myometrium was not included in the specimen, so invasion could not be commented upon. A differential of CM and EST was considered and more sampling was done. Subsequent sections revealed many thick-walled blood vessels. IHC for desmin was strongly positive, while CD 10 staining was negative, thereby confirming a diagnosis of CM.

Case 4

A 47-year-old female presented with discharge per vaginum, burning micturition off and on and constipation. Ultrasonography revealed a large mass in myometrium measuring 14 × 10 × 7.5 cm, suggestive of fibroid. Total abdominal hysterectomy with bilateral salpingoophorectomy was performed. Grossly, uterus measured 15 × 15 × 8 cm. On cutting, a large intramural mass was seen distorting the endometrial cavity with a solid, gray white cut surface. Microscopically, a well-circumscribed tumor was seen comprising of oval to spindle cells arranged in fascicles with round to oval nuclei. On further sectioning, few large thick-walled muscular vessels were found pointing towards a CM [Figure 4]. However, IHC for desmin and CD 10 was advised to rule out EST. Tumor cells were strongly positive

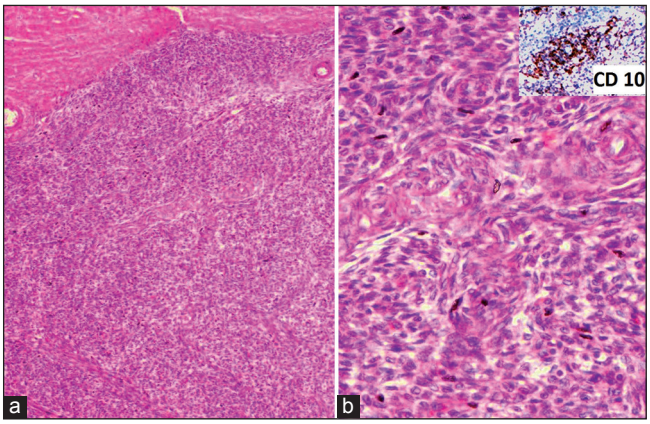

Figure 1: Photomicrograph shows a well-delineated tumor comprising of uniform, small, round nuclei with granular chromatin (a) ×100, hematoxylin andeosin and (b) ×400, hematoxylin andeosin); inset: Immunohistochemical stain for CD 10 shows strong cytoplasmic positivity (×100)

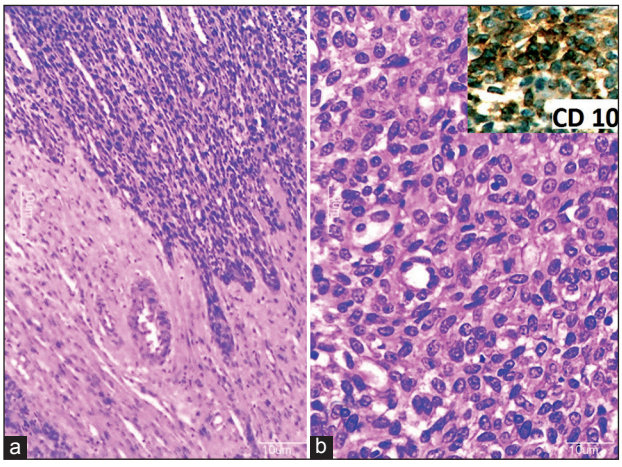

Figure 2: (a) Photomicrograph shows tumor cells arranged concentrically around spiral arteriole-like vessels with cord-like projections into myometrium (×100, hematoxylin andeosin); (b) Tumor cells are round to spindle-shaped, uniform-appearing cells with oval nuclei (×400, hematoxylin andeosin); inset: Immunohistochemical stain for CD 10 is strongly positive (×400)

for desmin and negative for CD 10, thus confirming a diagnosis of CM.

A comparative summary of salient features of all the cases is shown in Table 1.

DISCUSSION

Among the mesenchymal tumors of the uterus, uterine smooth muscle tumors and ESTs are the two major types, the latter being fairly uncommon. Although routine histopathological examination is sufficient to distinguish between ESS and smooth muscle tumors in most of the cases, the distinction between ESTs and highly CMs, on some occasions poses a great diagnostic challenge to the pathologist. This distinction is more important, but even more difficult in curetting (due to scanty material) or myomectomy specimens. Although a hysterectomy may be considered curative for a CM, but an ESS requires close follow-up and investigations to rule out any recurrence or metastasis.

The differentiation between EST and CM is necessary on account of several reasons. Firstly, the clinical course of the two tumors varies greatly. A highly CM follows a benign course usually while ESTs, especially ESS can behave aggressively. Secondly, the therapy for the two differentials, ESS and CM, also shows some variations. ESSs are usually ER positive, so respond to antiestrogen therapy. This would be useful, especially in metastatic ESS or extrauterine ESS; while for CM, myomectomy will suffice. Moreover, IHC also does not provide a foolproof solution to this problem as a completely endometrial stroma-specific IHC profile is not available. This could be due to the fact that both endometrium and myometrium arise from Mullerian duct, hence often express similar antigens with a considerable overlap between some markers. Additionally, endometrial stromal cells have the capacity to differentiate into well-

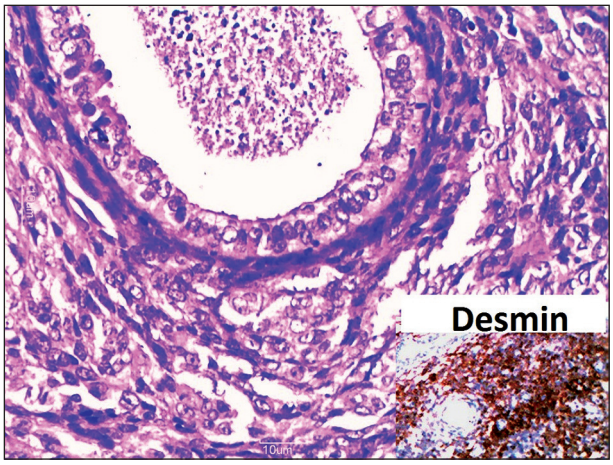

Figure 3: Photomicrograph shows plump to spindle tumor cells with moderate cytoplasm with round to oval nuclei arranged in fascicles around entrapped normal endometrial gland (×400, hematoxylin andeosin); inset: Immunohistochemical stain for desmin is strongly positive (×100)

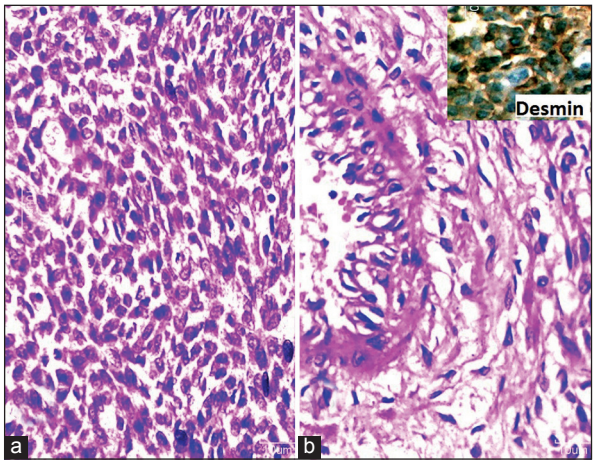

Figure 4: (a) Photomicrograph shows oval to spindle cells arranged in fascicles with round to oval nuclei (×400, hematoxylin andeosin), (b) thick-walled muscular artery seen (×400, hematoxylin and eosin); inset: Immunohistochemical stain for desmin showed strong cytoplasmic positivity (×400)

Table 1: Comparative summary of salient features of all the cases

Sr. no.	Age (years)	Clinical presentation	Clinical diagnosis	Specimen received	Histopathological differential diagnosis	IHC	Final diagnosis
Case 1	46	Menorrhagia, dull abdominal pain	Intramural fibroid	Hysterectomy; tumor size- 4.6×4.8 cm	ESN/CM	CD 10- diffuse positive;desmin negative	ESN
Case 2	39	Irregular bleeding per vaginum, acute retention of urine	Submucousfibroid polyp	Polypectomy followed by hysterectomy;tumor size- 9×8×8 cm	ESN/LGESS/CM	CD 10- diffuse positive;desmin negative	LGESS with sex cord differentiation
Case 3	40	Irregular heavy bleeding per vaginum	Cervical fibroid	Polypectomy;tumor size- 6×5×5 cm	CM/EST	Desmin-diffuse positive;CD 10 negative	CM
Case 4	47	Discharge per vaginum, burning micturition off and on, constipation	Fibroid	Hysterectomy;tumor size- 14×10×7.5 cm	CM	Desmin-diffuse positive;CD 10 -negative	CM

IHC: Immunohistochemistry, ESN: Endometrial stromal nodule, CM: Cellular leiomyomas, LGESS: Low-grade endometrial stromal sarcoma, EST: Endometrial stromal tumor

developed smooth muscle cells. So, smooth muscle actin (SMA), muscle-specific actin (MSA), and desmin may be expressed by both the tumors. Role of desmin as a discriminatory marker is also controversial; however, the consensus is that if desmin is diffusely and strongly positive, it favors a CM over an EST.[6]

Another diagnostic dilemma which may occur is when low-grade sarcomas exhibit other forms of differentiation, such as sex cord differentiation, as was seen in Case 2. Sex cord-like elements, arranged in nests, cords, trabeculae, solid, or tubular structures were seen; but only focally with inhibin positivity. If this element predominates, the tumor is considered to be a uterine tumor resembling ovarian sex cord tumor (UTROSCT), which may cause diagnostic difficulties. UTROSCT was first described by Clement and Scully in 1976.[11] UTROSCT is defined as a tumor with prominent sex cord-like differentiation in which there is no conspicuous endometrial stromal background. The clinical presentation and the gross appearance of both LGESS with sex cord-like differentiation and UTROSCT is similar. The pathologist, therefore, has an important role in differentiating UTROSCT from LGESS with sex cord-like differentiation on histopathological examination. The biological behaviors of these lesions are very different from each other and an accurate pathological diagnosis is critical. Frequent recurrences and metastases to the pelvic organs have been reported in LGESS, while UTROSCT behaves in a benign fashion.[12]

On routine histopathology, certain features have been proposed which help in resolving this dilemma to some extent. Features favoring a CM include the spindled shape of cells, fusiform shape of the nuclei, the reticulin pattern (parallel to fascicles of cells), and the absence of a plexiform vasculature.[2] Problem usually arises in cases without muscle or vascular invasion. Oliva *et al*.,[4] stressed upon the significance of finding large, thick-walled, muscular vessels as a pointer towards a CM rather than an EST.

The points to be considered in such settings include: Whether the differentiation is smooth muscle or endometrial stromal; whether the criteria for malignancy are evaluable; and whether the criteria for malignancy are met. Clinically, this becomes all the more important for young women who wish to retain their fertility.[2]

An important feature which complicates the differentiation between these two entities is the presence of foci of smooth muscle differentiation in around 10% of stromal nodules where tumor cells are embedded in hyalinized collagen giving it a starburst appearance. If the smooth muscle differentiation exceeds 30% of tumor, it should be classified as a combined stromal smooth muscle tumor.[1,2]

To conclude, routine histopathological features, namely, spindle cells with fusiform nuclei, presence of thick-walled vessels and reticulin pattern parallel to fascicles in CM, help in resolving the dilemma in most of the cases. Therefore, the need for extensive sampling of tumor should be reemphasized. IHC for CD 10, desmin, caldesmon, and inhibin also comes to the rescue in such indecisive cases and proves to be of great value in arriving at a definitive diagnosis.

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