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Review

Uterine sarcomas: A review

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ABSTRACT

Objective. Uterine sarcomas are rare tumors that account for 3% of uterine cancers. Their histopathologic classification was revised by the World Health Organization (WHO) in 2003. A new staging system has been recently designed by the International Federation of Gynecology and Obstetrics (FIGO). Currently, there is no consensus on risk factors for adverse outcome. This review summarizes the available clinicopathological data on uterine sarcomas classified by the WHO diagnostic criteria.

Methods. Medline was searched between 1976 and 2009 for all publications in English where the studied population included women diagnosed of uterine sarcomas.

Results. Since carcinosarcomas (malignant mixed mesodermal tumors or MMMT) are currently classified as metaplastic carcinomas, leiomyosarcomas remain the most common uterine sarcomas. Exclusion of several histologic variants of leiomyoma, as well as "smooth muscle tumors of uncertain malignant potential," frequently misdiagnosed as sarcomas, has made apparent that leiomyosarcomas are associated with poor prognosis even when seemingly confined to the uterus. Endometrial stromal sarcomas are indolent tumors associated with long-term survival. Undifferentiated endometrial sarcomas exhibiting nuclear pleomorphism behave more aggressively than tumors showing nuclear uniformity. Adenosarcomas have a favorable prognosis except for tumors showing myometrial invasion or sarcomatous overgrowth. Adenofibromas may represent well-differentiated adenosarcomas. The prognosis of carcinosarcomas (which are considered here in a post-script fashion) is usually worse than that of grade 3 endometrial carcinomas. Immunohistochemical expression of Ki67, p53, and p16 is significantly higher in leiomyosarcomas and undifferentiated endometrial sarcomas than in endometrial stromal sarcomas.

Conclusions. Evaluation of H&E stained sections has been equivocal in the prediction of behavior of uterine sarcomas. Immunohistochemical studies of oncoproteins as well as molecular analysis of non-random translocations will undoubtedly lead to an accurate and prognostically relevant classification of these rare tumors.

Contents

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Introduction

Uterine sarcomas are rare tumors that account for approximately 1% of female genital tract malignancies and 3% to 7% of uterine cancers [1]. Although the aggressive behavior of most cases is well recognized, their rarity and histopathological diversity has contributed to the lack of consensus on risk factors for poor outcome and optimal treatment [2].

Histologically, uterine sarcomas were first classified into carcinosarcomas, accounting for 40% of cases, leiomyosarcomas (40%), endometrial stromal sarcomas (10% to 15%), and undifferentiated sarcomas (5% to 10%). Recently, carcinosarcoma has been reclassified as a dedifferentiated or metaplastic form of endometrial carcinoma. Despite this, and probably because it behaves more aggressively than the ordinary endometrial carcinoma, carcinosarcoma is still included in most retrospective studies of uterine sarcomas, as well as in the 2003 World Health Organization (WHO) classification [3].

The 1988 International Federation of Gynecology and Obstetrics (FIGO) criteria for endometrial carcinoma have been used until now to assign stages for uterine sarcomas in spite of the different biologic behavior of both tumor categories. Recently, however, a new FIGO classification and staging system has been specifically designed for uterine sarcomas in an attempt to reflect their different biologic behavior (Table 1) [4]. Briefly, three new classifications have been developed: (1) staging for leiomyosarcomas and endometrial stromal sarcomas; (2) staging for adenosarcomas; and (3) staging for carcinosarcomas (MMMT). Whereas in the first classification stage I sarcomas are subdivided according to size, subdivision of stage I adenosarcomas takes into account myometrial invasion. On the other hand, carcinosarcomas will continue to be staged as endometrial carcinomas.

Table 1
FIGO staging for uterine sarcomas (2009).

Stage	Definition
(1) Leiomyosarcomas and endometrial stromal sarcomas[a]	
I	Tumor limited to uterus
IA	Less than or equal to 5 cm
IB	More than 5 cm
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
(2) Adenosarcomas	
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen).
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
(3) Carcinosarcomas	
Carcinosarcomas should be staged as carcinomas of the endometrium.	

[a] Note: Simultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

Leiomyosarcoma

Clinical features

After excluding carcinosarcoma (MMMT), leiomyosarcoma has become the most common subtype of uterine sarcoma. However, it accounts for only 1–2% of uterine malignancies. Most occur in women over 40 years of age who usually present with abnormal vaginal bleeding (56%), palpable pelvic mass (54%), and pelvic pain (22%). Signs and symptoms resemble those of the far more common leiomyoma and preoperative distinction between the two tumors may be difficult. Nevertheless, malignancy should be suspected by the presence of certain clinical behaviors, such as tumor growth in menopausal women who are not on hormonal replacement therapy [5]. Occasionally, the presenting manifestations are related to tumor rupture (hemoperitoneum), extrauterine extension (one-third to one-half of cases), or metastases. Only very rarely does a leiomyosarcoma originate from a leiomyoma.

Pathological features

The histopathologic diagnosis of uterine leiomyosarcoma is usually straightforward since most clinically malignant smooth muscle tumors of the uterus show the microscopic constellation of hypercellularity, severe nuclear atypia, and high mitotic rate generally exceeding 15 mitotic figures per 10 high-power-fields (MF/10 HPF) [6–7] (Fig. 1a). Moreover, one or more supportive clinicopathologic features such as peri- or postmenopausal age, extrauterine extension, large size (over 10 cm), infiltrating border, necrosis, and atypical mitotic figures are frequently present [8].

Epithelioid and myxoid leiomyosarcomas, however, are two rare variants which may be difficult to recognize microscopically as their pathologic features differ from those of ordinary spindle cell leiomyosarcomas. In fact, nuclear atypia is usually mild in both tumor

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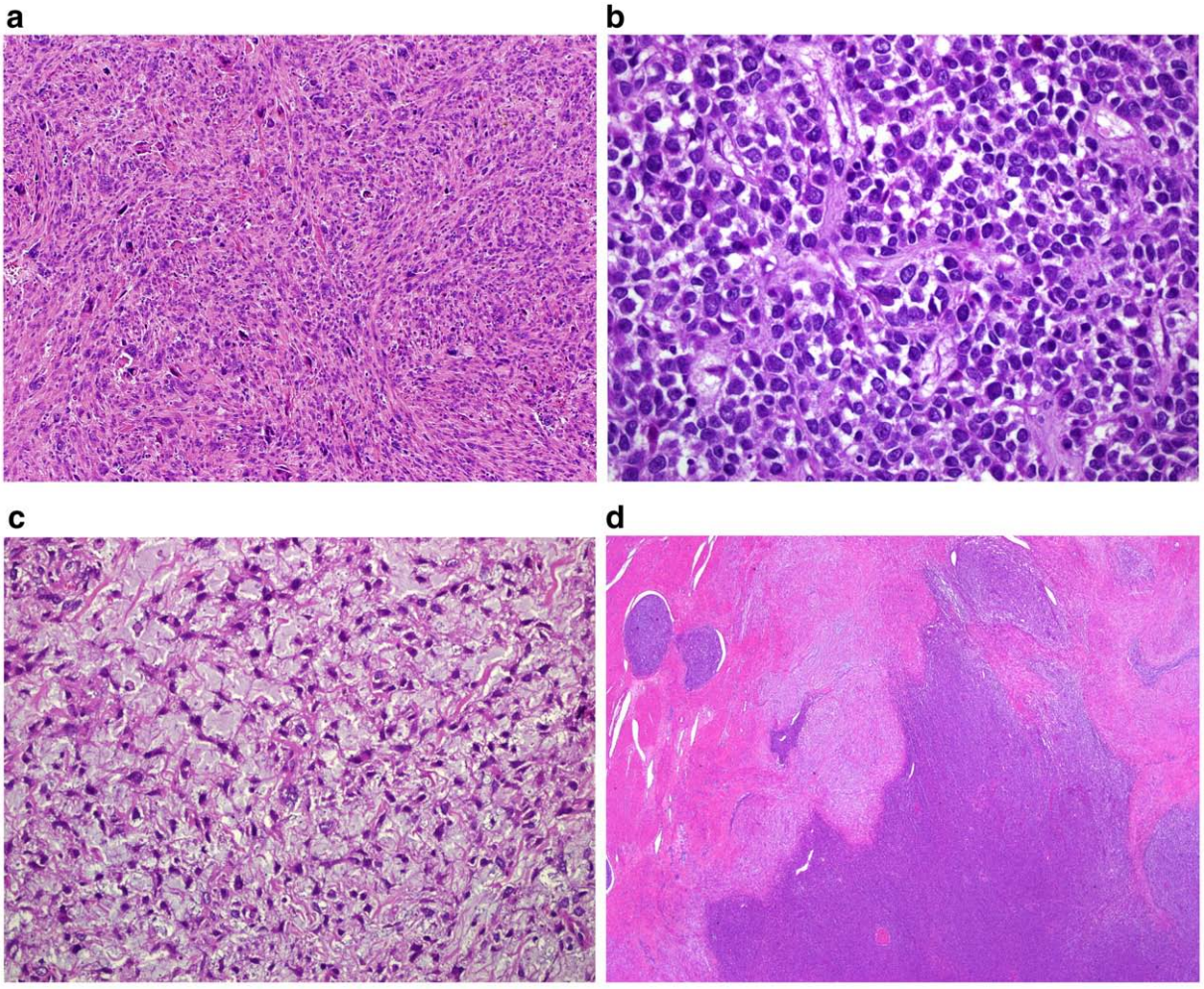

Fig. 1. (a) Leiomyosarcoma, spindle-cell variant; (b) myxoid leiomyosarcoma; (c) epithelioid leiomyosarcoma; (d) endometrial stromal sarcoma.

types and the mitotic rate is often <3 MF/10 HPF [9] (Figs. 1b, c). In epithelioid leiomyosarcomas, necrosis may be absent and myxoid leiomyosarcomas are often hypocellular. In the absence of severe cytologic atypia and high mitotic activity, both tumors are diagnosed as sarcomas based on their infiltrative borders [10].

The minimal pathological criteria for the diagnosis of leiomyosarcoma are more problematic and, in such cases, the differential diagnosis has to be made, not only with a variety of benign smooth muscle tumors that exhibit atypical histologic features and unusual growth patterns (Table 2), but also with smooth muscle tumors of uncertain malignant potential (STUMP) (Table 3). Application of the 2003 WHO diagnostic criteria [4] has allowed distinguishing these unusual histologic variants of leiomyoma frequently misdiagnosed as well-differentiated or low-grade leiomyosarcomas in the past. Indeed, in a recent population-based study of uterine sarcomas from Norway [11], of 356 tumors classified initially as leiomyosarcomas, diagnosis was confirmed in only 259 cases (73%), whereas 97 (27%) were excluded on review and reclassified as leiomyomas or leiomyoma variants. Follow-up information, however, revealed that 4 of 48 excluded tumors (1 cellular leiomyoma and 3 STUMPs) developed metastases.

Table 2
Benign smooth muscle tumors of the uterus.

Leiomyoma variants that may mimic malignancy	Smooth muscle proliferations with unusual growth patterns
• Mitotically active leiomyoma	• Disseminated peritoneal leiomyomatosis
• Cellular leiomyoma	• Benign metastasizing leiomyoma
• Hemorrhagic leiomyoma and hormone-induced changes	• Intravenous leiomyomatosis
• Leiomyoma with bizarre nuclei (atypical leiomyoma)	• Lymphangioleiomyomatosis
• Myxoid leiomyoma	
• Epithelioid leiomyoma	
• Leiomyoma with massive lymphoid infiltration	

Immunohistochemistry and molecular biology

Recently, several immunohistochemical and molecular genetic studies on uterine leiomyosarcomas have been reported [12,13–19]. Leiomyosarcomas usually express smooth muscle markers such as desmin, h-caldesmon, smooth muscle actin, and histone deacetylase 8 (HDCA8). However, it is important to keep in mind that epithelioid and myxoid leiomyosarcomas may show lesser degrees of immunoreaction for these markers. Also, leiomyosarcomas are often immunoreactive for CD10 and epithelial markers including keratin and EMA

Table 3
Smooth muscle tumors of uncertain malignant potential (STUMP).

Pathologic criteria
• Tumor cell necrosis in a typical leiomyoma
• Necrosis of uncertain type with ≥10 MF/10 HPFs, or marked diffuse atypia
• Marked diffuse or focal atypia with borderline mitotic counts
• Necrosis difficult to classify

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(the latter being more frequently positive in the epithelioid variant). Conventional leiomyosarcomas express estrogen receptors (ER), progesterone receptors (PR), and androgen receptors (AR) in 30-40% of cases. Whereas a variable proportion of uterine leiomyosarcomas has been reported as being immunoreactive for c-KIT, no c-KIT mutations have been identified [20].

Recent studies have shown statistically significant higher levels of Ki67 in uterine leiomyosarcomas compared with benign smooth muscle tumors [15–19]. Mutation and overexpression of p53 have been described in a significant minority of uterine leiomyosarcomas (25-47%) but not in leiomyomas [15,18,19]. Intermediate rates have been found in atypical leiomyomas and STUMPs. Overexpression of p16 has been described in uterine leiomyosarcomas and may prove to be a useful adjunct immunomarker for distinguishing between benign and malignant uterine smooth muscle tumors [13–15].

The vast majority of uterine leiomyosarcomas are sporadic. Patients with germline mutations in fumarate hydratase are believed to be at increased risk for developing uterine leiomyosarcomas as well as uterine leiomyomas [21,22]. The oncogenic mechanisms underlying the development of uterine leiomyosarcomas remain elusive. Overall, uterine leiomyosarcoma is a genetically unstable tumor that demonstrates complex structural chromosomal abnormalities and highly disturbed gene regulation which likely reflects the end-state of accumulation of multiple genetic defects. Extrapolating from experiences in soft tissue leiomyosarcomas, it is unlikely that recurrent disease-driven genetic aberrations (i.e. gene mutation or translocation events) will be uncovered. In comparison with other more common uterine malignancies, uterine leiomyosarcomas bear some resemblance to type 2 endometrial carcinomas and high-grade serous carcinomas of ovary/fallopian tube origin, based on their genetic instability, frequent p53 abnormalities, aggressive behavior, and resistance to chemotherapy. Therefore, therapies that exploit the underlying genetic instability of uterine leiomyosarcomas may prove to be an effective therapeutic strategy.

Prognosis and treatment

Leiomyosarcomas are very aggressive tumors. It has become apparent that tumors diagnosed according to the 2003 WHO criteria are associated with poor prognosis even when confined to the uterus [11,23] and even when diagnosed at an early stage; recurrence rate has ranged from 53% to 71% [1]. First recurrences were in the lungs in 40% of patients and in the pelvis in only 13%. Overall survival rate ranged from 15% to 25% with a median survival of only 10 months in one study. In the Norwegian series [11], patients with leiomyosarcomas limited to the uterus had poor prognosis with a 5-year overall survival of 51% at stage I and 25% at stage II (by the 1988 FIGO staging classification). All patients with spread outside the pelvis died within 5 years.

There has been no consistency among various studies regarding correlation between survival and patient age, clinical stage, tumor size, type of border (pushing versus infiltrative), presence or absence of necrosis, mitotic rate, degree of nuclear pleomorphism, and vascular invasion [2,12,23–29]. One study, however, found tumor size to be a major prognostic parameter [2]: five of 8 patients with tumors <5 cm in diameter survived, whereas all patients with tumors >5 cm in diameter died of tumor. In this study of 208 uterine leiomyosarcomas, the only other parameters predictive of prognosis were tumor grade and stage [2]. Histologic grade, however, has not been consistently identified as a significant prognostic parameter. In the report from Norway [11], including 245 leiomyosarcomas confined to the uterus, tumor size and mitotic index were significant prognostic factors and allowed for separation of patients into 3 risk groups with marked differences in prognosis. Ancillary parameters including p53, p16, Ki 67, and Bcl-2 have been used in leiomyosarcomas trying to predict outcome [23]. However, it is not clear whether they act independently of stage which still is the most significant prognostic factor for uterine sarcomas.

Treatment of leiomyosarcomas includes total abdominal hysterectomy and debulking of tumor if present outside the uterus. Removal of the ovaries and lymph node dissection remain controversial as metastases to these organs occur in a small percentage of cases and are frequently associated with intra-abdominal disease [2]. Ovarian preservation may be considered in premenopausal patients with early-stage leiomyosarcomas [2]. Lymph node metastases have been identified in 6.6% and 11% of two series of patients with leiomyosarcoma who underwent lymphadenectomy [2,30]. In the first series, the 5-year disease-specific survival rate was 26% in patients who had positive lymph nodes compared with 64.2% in patients who had negative lymph nodes ($p<0.001$) [30]. The influence of adjuvant therapy on survival is uncertain. Radiotherapy may be useful in controlling local recurrences and chemotherapy with doxorubicin or docetaxel/gemcitabine is now used for advanced or recurrent disease, with response rates ranging from 27% to 36% [31,32]. Some patients may respond to hormonal treatment [33].

Smooth muscle tumors of uncertain malignant potential (STUMP)

Uterine smooth muscle tumors that show some worrisome histological features (i.e., necrosis, nuclear atypia, or mitoses), but do not meet all diagnostic criteria for leiomyosarcoma, fall into the category of STUMP (Table 3) [3,34]. The diagnosis of STUMP, however, should be used most sparingly and every effort should be made to classify a smooth muscle tumor into a specific category [3,34]. Most tumors classified as STUMP have been associated with favorable prognosis and, in these cases, only follow-up of the patients is recommended [35]. In fact, in a recent study of 41 cases of STUMP, the recurrence rate was 7%. One of the two recurrences was in the form of STUMP and the other as leiomyosarcoma [36].

Endometrial stromal tumor

Endometrial stromal tumors are the second most common pure mesenchymal tumors of the uterus even though they account for less than 10% of all such tumors. According to the latest WHO classification [3], the term endometrial stromal tumor is applied to neoplasms typically composed of cells that resemble endometrial stromal cells of the proliferative endometrium [3]. They are divided into: endometrial stromal nodules, low-grade endometrial stromal sarcomas, and undifferentiated endometrial sarcomas.

Endometrial stromal nodule

These rare tumors are composed of cells reminiscent of proliferative-phase endometrial stromal cells. They occur at any age during reproductive or later years. Most are incidental findings in a hysterectomy specimen while others present with abnormal uterine bleeding.

The tumors are typically round and well-circumscribed but not encapsulated. They are usually solitary, ranging from under 1 to 22 (mean 7) cm. If located in the endometrium, they are frequently polypoid; however, they may be intramyometrial or subserosal. They have a uniform soft, yellow cut surface which does not show the whorled pattern characteristic of a leiomyoma. Cysts may be present.

The main distinguishing feature of endometrial stromal nodules is their expansile, non-infiltrating, smooth margin that contrasts with the infiltrating irregular margin of stromal sarcomas [37]. Focal irregularities in the form of lobulated or finger-like projections into the adjacent myometrium not exceeding 3 mm and not exceeding 3 in number may be seen [38]. Vascular invasion should not be present.

Endometrial stromal nodules have an excellent prognosis and patients are cured by hysterectomy [39]. Conservative treatment with

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excision of the mass is performed only when complete examination of the margins can be done which only occurs in rare instances [40].

Low-grade endometrial stromal sarcoma

Endometrial stromal sarcomas account for approximately 0.2% of all malignant uterine tumors and 10-15% of uterine malignancies with a mesenchymal component. They occur in women between 40 and 55 years of age. Some cases have been reported in patients with ovarian polycystic disease, after estrogen use, or tamoxifen therapy. Patients commonly present with abnormal uterine bleeding, pelvic pain, and dysmenorrhea but as many as 25% of them are asymptomatic [41]. At presentation, extrauterine pelvic extension, most commonly involving the ovary, is found in up to 1/3 of patients. Thus, when evaluating an ovarian tumor microscopically consistent with an endometrial stromal tumor, it is important to exclude a prior history of uterine endometrial stromal tumor and to suggest inspection of the uterus, as the latter are far more common.

Grossly, there is irregular nodular growth involving the endometrium, myometrium, or both. The main mass is frequently associated with varying degrees of permeation of the myometrium, including worm-like plugs of tumor that fill and distend myometrial veins, frequently extending to parametrial veins and lymphatics. Microscopically, endometrial stromal sarcomas exhibit only mild nuclear atypia. Mitotic activity is typically <5 MF/10 HPF. Necrosis is rarely seen (Fig. 1d).

Immunohistochemistry and molecular biology

Endometrial stromal nodules and low-grade endometrial stromal sarcomas are typically immunoreactive for vimentin, muscle-specific actin, alpha-smooth muscle actin, and frequently keratin [42–44]. Most endometrial stromal tumors as well as normal endometrial stromal cells stain for CD10. However, smooth muscle tumors, mixed mullerian tumors or even rhabdomyosarcomas may also be immunoreactive for CD10 [42–44]. Thus, this antibody should not be used in isolation when evaluating the cell of origin in a uterine mesenchymal tumor. Not uncommonly, endometrial stromal tumors can exhibit diffuse alpha-smooth muscle actin reactivity, while desmin and h-caldesmon are generally negative or at most focally positive [44]. Other muscle markers including myosin and HDCA8 are also helpful in this differential diagnosis [45]. Areas of smooth muscle differentiation are reactive for all smooth muscle markers as well as for CD10. Areas of sex cord-like differentiation may be reactive for inhibin, calretinin, CD99, WT-1, and Melan A. [46] Endometrial stromal tumors frequently contain ER and PR and they also frequently express beta-catenin [47]. Endometrial stromal sarcomas often carry the translocation t(7;17) with involvement of two zinc finger genes, JAZF1 and JJAZ1, suggesting a genetic basis for tumor development [48].

Prognosis and treatment

Endometrial stromal sarcomas are indolent tumors with a favorable prognosis [38]. Tumor behavior is characterized by late recurrences even in patients with stage I disease; thus, long term follow-up is required. About one third of patients develop recurrences, most commonly in the pelvis and abdomen, and less frequently in the lung and vagina [41].

The outcome in patients with endometrial stromal sarcomas depends largely on the extent of the tumor at the time of diagnosis. Surgical stage higher than I is a univariate predictor of unfavorable outcome. Generally endometrial stromal sarcomas have good prognosis, with 5- and 10-year actuarial survival for patients with stage I tumors of 98% and 89%, respectively [41]. Several other features may help predict outcome. Clinicopathologic factors reported in the older literature to be of potential prognostic importance included age, race, size, FIGO stage, depth of myometrial invasion, tumor grade, mitotic activity, and DNA ploidy [49–52]. However, in the largest study of low-grade endometrial stromal sarcomas, mitotic activity and cytologic atypia were not found to be predictive of tumor recurrence in stage I tumors (most common scenario), while size correlated poorly with outcome as tumors <4 cm in diameter also recurred [41]. In another recent study [11], prognosis of endometrial stromal sarcomas confined to the uterus (83 cases) was related to mitotic index and tumor cell necrosis.

Treatment of endometrial stromal sarcomas is largely surgical in the form of hysterectomy and bilateral salpingo-oophorectomy. These tumors are often sensitive to hormones and it has been stated that patients retaining their ovaries have a higher risk of recurrence [53]; however, there is no complete agreement on this issue [50,53–56]. Although lymph node metastases have been found in 7% of 384 women with low-grade endometrial stromal sarcoma, this finding does not affect the excellent overall survival of these patients [54]. Patients may receive also adjuvant radiation or hormonal treatment with progestational agents or aromatase inhibitors [57,58].

Undifferentiated endometrial sarcoma

Clinicopathological features

The diagnosis of undifferentiated endometrial sarcoma is applied to tumors that exhibit myometrial invasion, severe nuclear pleomorphism, high mitotic activity, and/or tumor cell necrosis, and lack smooth muscle or endometrial stromal differentiation [3]. Grossly, they are often polypoid and show a fleshy, gray to white cut surface and prominent areas of hemorrhage and necrosis. On microscopic examination, there is destructive myometrial invasion while the intravascular worm-like plugs characteristic of low-grade endometrial stromal sarcomas are typically absent. They have marked cellular pleomorphism and brisk mitotic activity, almost always exceeding 10 MF/10HPF and sometimes approaching 50 MF/10HPF. Extensive necrosis is frequently present. These tumors should be diagnosed only after extensive sampling has excluded smooth or skeletal muscle differentiation or even small foci of carcinoma, as this finding would result in a diagnosis of carcinosarcoma. The histological appearance of this tumor is more like the mesenchymal elements of a carcinosarcoma than a typical endometrial stromal tumor [3]. Occasional tumors have a component of low-grade endometrial stromal sarcoma indicating that the high-grade component is presumably of endometrial stromal derivation. A recent study [59] has divided high-grade tumors into two categories based on nuclear uniformity and has proposed that undifferentiated endometrial sarcomas showing nuclear regularity may represent an intermediate subcategory of endometrial stromal tumors (formerly classified as high-grade endometrial stromal sarcomas) that shares some immunohistochemical and molecular features with low-grade endometrial stromal sarcoma and is associated with better outcome than undifferentiated sarcomas exhibiting nuclear pleomorphism [59].

Immunohistochemistry

Undifferentiated endometrial sarcomas lack immunoreaction for ER and PR, but a high proportion is EGFR immunoreactive [3]. CD10 expression is not helpful in the differential diagnosis with other uterine sarcomas because undifferentiated endometrial sarcoma as well as leiomyosarcoma, rhabdomyosarcoma, and carcinosarcoma may express this marker. Smooth muscle markers and myogenin or myoD1 may be used to rule out leiomyosarcoma or rhabdomyosarcoma respectively, or to identify a rhabdomyosarcomatous component of a carcinosarcoma.

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Prognosis and treatment

Undifferentiated endometrial sarcomas have very poor prognosis and most patients die of disease within two years of the diagnosis. In a recent study [11], vascular invasion was the only statistically significant prognostic factor, with a 5-year crude survival of 83% and 17% when vascular invasion was absent or present, respectively ($P = 0.02$). Local recurrences and distant metastases are associated with a high mortality. Treatment is primarily surgical with or without addition of adjuvant radiotherapy or chemotherapy [60,61].

Adenosarcoma

Clinical features

The rare mullerian adenosarcoma is a mixed tumor of low malignant potential with distinctive clinicopathologic features [62]. It occurs mainly in the uterus of postmenopausal women but also in adolescents and young adults and in extrauterine locations [62]. The most common presenting symptom is abnormal vaginal bleeding but some patients present with pelvic pain, an abdominal mass or vaginal discharge. Some patients have taken tamoxifen therapy or have had prior radiation therapy. Most commonly, adenosarcomas arise from the endometrium, including the lower uterine segment, but rare tumors arise in the endocervix and within the myometrium, probably from adenomyosis. Rarely, adenosarcomas have an extrauterine location and involve the ovary, pelvic tissues, or intestinal serosa.

Pathological features

The uterine cavity is typically filled and distended by a soft polypoid and sometimes large mass which may project through the cervical os. The cut surface may show variably sized cysts or clefts. There is often focal hemorrhage and necrosis. The margin of the tumor is usually well defined.

Microscopically, it shows an intimate admixture of benign but sometimes atypical glandular epithelium and low-grade sarcoma, usually of endometrial stromal type. Typically, the glands are cystic and the stroma concentrates around them forming periglandular cuffs (Figs. 2a, b). The histologic picture is reminiscent of a phyllodes tumor of the breast. Although the mean mitotic rate is 9 MF/10 HPF [62], in the presence of hypercellular periglandular cuffs, only 2 MF/10 HPF are enough for the diagnosis [62]. Most adenosarcomas show only mild to moderate nuclear atypia in the stromal component. Heterologous mesenchymal elements (usually rhabdomyosarcoma, but also cartilage, fat, and other elements) are found in 10–15% of cases. Vaginal or pelvic recurrence, estimated to occur in about 25–30% of cases at 5 years, is associated almost exclusively with myometrial invasion and sarcomatous overgrowth [62]. Myometrial invasion is found in 15% of cases, but deep invasion in only 5%. Sarcomatous overgrowth defined as the presence of pure sarcoma, usually of high-grade and without a glandular component, occupying

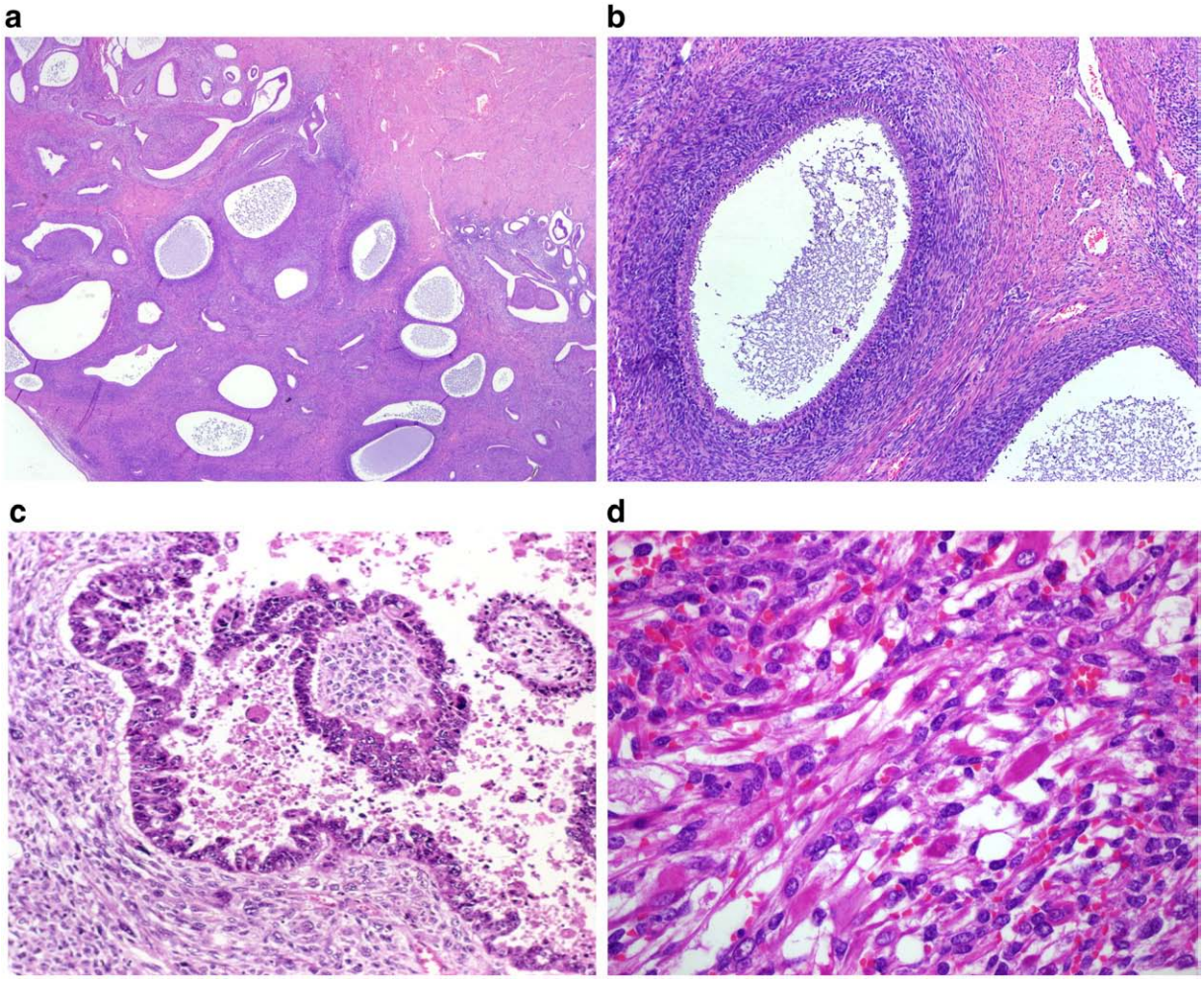

Fig. 2. (a) Adenosarcoma; (b) periglandular cuffing in adenosarcoma; (c) carcinosarcoma; (d) Rhabdomyosarcoma component in carcinosarcoma.

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at least 25% of the tumor, has been reported in 8–54% of uterine and 30% of ovarian adenosarcomas [62].

Adenosarcoma versus adenofibroma

Adenosarcomas are low-grade neoplasms classified halfway along the spectrum of mixed mullerian tumors, with adenofibromas at one end and carcinosarcomas at the other. Whereas the histologic diagnosis of the latter is usually straightforward, distinction between adenosarcoma and its rarer benign counterpart, the adenofibroma, may be difficult. A recent study [63] has shown that some clinically malignant tumors without sarcomatous overgrowth may exhibit only moderate stromal cellularity with focal periglandular cuffs, low mitotic count (<2 MFs/10 HPF) and mild nuclear atypia. The finding of such cases raise the question whether or not adenofibroma exists as a tumor entity. In this study, immunoreaction for several tumor markers was similar both in typical adenosarcomas and adenofibromas associated with favorable outcome. Thus, it was suggested that some of so-called "adenofibromas" may in fact represent exceedingly well differentiated adenosarcomas [63].

Immunohistochemistry

In most adenosarcomas without sarcomatous overgrowth, the immunophenotype of the stromal component resembles that of an endometrial stromal sarcoma. In cases with sarcomatous overgrowth, the mesenchymal component exhibits a higher Ki-67 proliferation, p53 immunoreaction and there is usually loss of expression of ER, PR and CD10. The immunophenotype is similar to that of a high-grade uterine sarcoma [63,64] and DNA is aneuploid [65].

Prognosis and treatment

Except when associated with myometrial invasion or sarcomatous overgrowth, the prognosis of adenosarcoma is far more favorable than that of carcinosarcoma; however, about 25% of patients with adenosarcoma ultimately die of their disease [62]. Recurrences usually occur in the vagina, pelvis, or abdomen. They may be late, for which reason long-term follow-up is needed. Local recurrences and distant metastases, which occur in 5% of cases, are almost always composed of pure sarcoma (70%). Treatment of choice is total abdominal hysterectomy with bilateral salpingo-oophorectomy. In the series from Norway [11], which included 23 adenosarcomas, tumor cell necrosis was the strongest prognostic factor ($P = 0.006$).

Carcinosarcoma (malignant mixed mullerian tumor)

Clinical features

Carcinosarcoma, also referred to as "malignant mixed mullerian tumor," is a biphasic neoplasm composed of distinctive and separate, but admixed, malignant-appearing epithelial and mesenchymal elements (Fig. 2c). It accounts for almost half of all uterine sarcomas [65,66]. Although they occur typically in post-menopausal women, a small number has been reported in patients less than 40 years of age. Most women present with abnormal vaginal bleeding and uterine enlargement. The serum level of CA125 is elevated in most cases. At presentation, extrauterine spread (stages III–IV) is found in up to 1/3 of cases. Up to 37% of patients with carcinosarcomas have a history of pelvic irradiation. These tumors tend to occur in younger women, often contain heterologous elements, and are found at advanced stage [67].

Pathological features

Carcinosarcomas are typically large, bulky polypoid masses, filling the uterine cavity and prolapsing through the cervical os. The cut surface is usually fleshy and often shows areas of hemorrhage, necrosis, and cystic change. Myometrial invasion is frequently seen. Rare tumors may arise in the uterine cervix. On microscopic examination, the carcinomatous component is usually serous (two-thirds of cases) or endometrioid (one-third) but, rarely, it may be clear cell, mucinous, or squamous cell carcinoma. In a recent study, 10% of the carcinomatous components were FIGO grade 1, 10% grade 2, and 80% grade 3 [66]. The sarcomatous components are heterogeneous. The homologous components of carcinosarcoma are usually spindle cell sarcoma without obvious differentiation; many resemble fibrosarcomas or pleomorphic sarcomas. Almost all are high grade sarcomas. The most common heterologous elements are malignant skeletal muscle or cartilage resembling either pleomorphic rhabdomyosarcoma or embryonal rhabdomyosarcoma [66] (Fig. 2d).

Histogenesis

Recently, it has been proposed that carcinosarcomas may represent metaplastic carcinomas [66–68]. Findings that support this hypothesis include: (a) frequent association of carcinosarcomas with otherwise typical endometrial adenocarcinomas within the same hysterectomy specimen; (b) frequent recurrence of carcinosarcomas as pure adenocarcinomas; (c) occasional recurrence of apparently pure endometrial adenocarcinomas as carcinosarcomas; and (d) similar metastatic pattern of carcinosarcomas and endometrial adenocarcinomas. Nevertheless, from a managerial viewpoint, it should be emphasize that carcinosarcomas have distinctive clinical and pathological features which warrant their separation from endometrial carcinomas; i.e., they are highly aggressive tumors and fatal in the vast majority of cases. Unlike metaplastic carcinomas in other sites, there is usually no merging of the two components of carcinosarcomas at either histological or ultrastructural [69] levels and heterologous mesenchymal elements are common.

Immunohistochemistry

The immunophenotype parallels that of the individual elements; i.e., the serous component should express cytokeratins, epithelial membrane antigen (EMA), and p53, while the rhabdomyoblastic elements should express desmin, myogenin, or MyoD1. However, it is well known that the sarcomatous component can express cytokeratins (as in leiomyosarcomas) and the epithelial component is often immunoreactive for vimentin (as in endometrial carcinomas). Such findings reflect the common mesodermal origin of these tumors. The homologous component can also express CD10, a marker used initially for the diagnosis of endometrial stromal tumors. In most cases, immunohistochemistry is not needed for diagnosis and should only be used to confirm the presence of rhabdomyoblasts.

Prognosis and treatment

Carcinosarcomas are highly aggressive tumors, far more aggressive than usual endometrial carcinomas. The overall 5-year survival for patients with carcinosarcoma is around 30% and for those with stage I (confined to the corpus) approximately 50% [1,66–69]. This is in contrast with that of other high grade endometrial cancers for which 5-year survival in stage I disease is approximately 80% or better [70,71]. Surgical stage and, particularly, depth of myometrial invasion are the most important prognostic indicators. Myometrial invasion beyond the inner third is seen in 80% of tumors and 40% show deep myometrial invasion. However, confinement to an endometrial polyp in absence of myometrial invasion does not preclude extrauterine spread. Lymphatic and blood vessel invasion are found in most cases. Metastatic and recurrent tumors may exclusively be carcinomatous, sarcomatous, or mixed, but they are often predominantly carcinomatous [66,69]. Tumors containing serous and clear cell carcinoma are

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thought to be associated with higher frequency of metastases, deep myometrial invasion, lymphatic or vascular space invasion, and cervical involvement [68]. In common with the older literature, a recent study has found that the presence of heterologous elements is a statistically significant poor prognostic factor in stage I patients [66].

Appropriate treatment includes total abdominal hysterectomy with bilateral salpingo-oophorectomy, removal of pelvic and aortic lymph nodes, omentectomy, and peritoneal cytology. The role of adjuvant radiotherapy and chemotherapy is uncertain but some studies have demonstrated the advantage of radiotherapy for disease-specific survival in early-stage tumors as well as local control in advanced-stage tumors. Taxanes and cisplatin-based chemotherapy as well as ifosphamide, along with whole pelvic irradiation, may lead to increased survival in patients with metastatic carcinosarcomas [72–74].

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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