

Malignant mixed Müllerian tumors of the uterus: sonographic spectrum

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ABSTRACT

Objective To describe the sonographic findings for malignant mixed Müllerian tumors (MMMTs) of the uterus with particular emphasis on their features on saline contrast sonohysterography (SCSH) and color Doppler sonography, and to determine how they relate to pathological findings.

Methods The SCSH and color Doppler findings in 29 histologically proven cases of uterine MMMT were reviewed retrospectively and their relationship to gross and histological findings were investigated.

Results Of the 29 uterine tumors, 16 were located only in the corpus, nine only in the fundus and four in both the corpus and fundus. Mean tumor size was 5.4 cm. The most common appearance was a polypoid mass projecting into the endometrial cavity, found in 23 cases. Twenty-eight tumors had an irregular surface, which was papillary in 20 cases and lobulated in eight. Most appeared heterogeneously isoechoic (n = 16) or hypoechoic (n = 12), occasionally with a trabecular appearance, and they often had clefts or fissure-like cystic areas (n = 10), necrosis (n = 4) or hemorrhagic areas (n = 7). Myometrial invasion was present in 27 cases and dilatation of the endometrial cavity was seen in 11. Color Doppler sonography showed moderate to marked vascularity in 20 out of the 24 cases in which it was performed, with a mean resistance index of 0.41, and appeared as feeding (n = 15) or randomly dispersed (n = 9) vessels.

Conclusions Uterine MMMTs have distinct sonographic features that are related to pathological findings. Knowledge of the sonographic appearance of MMMTs may facilitate diagnosis. Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Uterine malignant mixed Müllerian tumor (MMMT), also known as carcinosarcoma, is rarely encountered and accounts for only 1–3% of all uterine malignant tumors. It is a biphasic tumor that has both epithelial and stromal components. These tumors usually occur in elderly postmenopausal women, and tamoxifen treatment and prior pelvic radiotherapy have recently been recognized to be risk factors for the development of MMMT^{1–6}.

Preoperative diagnosis of MMMT is important because the disease is usually diagnosed at an advanced stage with myometrial invasion and metastasis; hence, MMMT is associated with a poor prognosis. However, it is difficult to make the differential diagnosis of this tumor because of its rarity and lack of specific imaging features that might distinguish it from other malignant uterine tumors, including the more common endometrial carcinoma. Accordingly, the majority of MMMTs are diagnosed according to histological findings following endometrial curettage⁷.

A few case reports have described the sonographic appearance of MMMT. These reports describe a large, heterogeneous or hyperechoic intracavitary mass with dilatation of the endometrial cavity, or a diffuse mass replacing the uterus. Masses often have anechoic cystic areas or necrosis and prominent vascularity with randomly dispersed vessels. However, these are nonspecific findings, and overlap with endometrial carcinoma and other uterine sarcoma types^{7–14}.

To the best of our knowledge, no review on the broad spectrum of sonographic appearances possible in uterine MMMTs has been undertaken, nor has any study been performed to investigate the relationship between sonographic features of MMMTs and histopathological findings to aid in the differentiation between MMMTs and other uterine tumors.

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In this study, we aimed to describe the sonographic findings for MMTs of the uterus, with particular emphasis on their features on saline contrast sonohysterography (SCSH) and color Doppler sonography, and to review the literature describing these features of uterine MMTs. Furthermore, we aimed to determine the relationship between these findings and histopathological findings.

PATIENTS AND METHODS

Between March 2003 and May 2011, 29 women were histologically confirmed to have MMT of the uterus at our institution. The average patient age was 61.1 (range, 33–69) years. The majority of patients were postmenopausal, and of the four premenopausal patients, one presented with polycystic ovarian disease. Patients with a history of estrogen replacement therapy, tamoxifen treatment or pelvic radiotherapy prior to imaging were excluded. Vaginal bleeding was present in 24 patients, vaginal discharge in two, pelvic pain in two and abdominal distension with weight loss in one. Serum CA-125 level was elevated in seven of the 26 patients tested, and results ranged from 40.7 to 1886 U/mL.

All 29 patients were examined by transvaginal sonography (TVS) and SCSH, and 24 were examined by color Doppler sonography prior to SCSH, using an Acuson Sequoia 512 system (Siemens Medical Solutions, Mountain View, CA, USA) with a 4–8-MHz endovaginal probe. Doppler parameters were adjusted as appropriate for optimal detection of low-velocity flow: Doppler frequency was 4–5 MHz; color gain was set at 40–50% with medium persistence; spatial peak temporal average intensity was set at c. 40–80 mW/cm²; the wall filter was set at 50–100 Hz; the pulse repetition frequency was set between 5 and 17 KHz; the velocity range was set at 4–20 cm/sec; the angle of insonation was maintained at < 60°; and the sample volume was 1–3 mm.

The sonographic findings of these tumors according to TVS and SCSH were evaluated retrospectively for the following characteristics: tumor location in corpus, fundus, or both; size; growth pattern (pedunculated, polypoid or broad-based sessile); surface (smooth or irregular, either lobulated or papillary); margins with underlying myometrium (ill-defined or well-circumscribed); echogenicity compared with myometrium (hyperechoic, isoechoic or hypoechoic) and echotexture (homogeneous or heterogeneous); the presence of cysts, hemorrhagic foci or necrosis; dilatation of the uterine cavity with fluid collection; the presence of myometrial invasion; and the presence of invasions to the cervix, adnexa and cul-de-sac. The tumor size was measured at its greatest diameter. Besides the presence of intratumoral cysts, ill-defined hypoechoic areas were understood to be suggestive of necrosis or hemorrhage. Myometrial invasion was determined by the poorly-defined endometrial–myometrial interface and the depth of myometrial invasion was classified into two categories according to previously defined criteria: superficial invasion of less than half of the myometrium and deep invasion of half of the

myometrium or more. Direct tumor extension to the cervical stroma, and a discrete mass in the ovary or tube and on the peritoneal surface in the cul-de-sac were diagnosed as tumor invasion.

Tumor vascularity (mild, moderate or marked), vascular pattern (single or multiple, feeding or randomly dispersed vessels) and resistance index (RI) were also determined by color Doppler sonography. The RI of arterial flow in the main feeding and intralesional vessels was recorded as the mean of measurements obtained from a minimum of three Doppler waveforms.

Surgical staging and pathological assessments were performed within 2 weeks of sonographic studies for all patients; nine patients had Stage Ia disease, six had Stage Ib, three Stage IIIa, five Stage IIIc and six Stage IVb. The pathological diagnoses of epithelial carcinoma in the 29 patients included 23 endometrioid adenocarcinomas, four papillary serous carcinomas, one mixed carcinoma, and one neuroendocrine carcinoma. The malignant stromal component was of the homologous type in 18 cases as endometrial stromal sarcoma or leiomyosarcoma, and was of the heterologous type in 11 cases as rhabdomyosarcoma, chondrosarcoma, osteosarcoma or liposarcoma. Pathological records of gross and histologic findings were corroborated with sonographic findings. The study was approved by our Institutional Review Board.

RESULTS

TVS and SCSH revealed that 16 of the total 29 uterine tumors were only in the uterine corpus, nine were only in the fundus and four were in both the corpus and fundus. Tumor size ranged from 2.6 to 17 (mean, 5.4) cm. The most common appearance was a polypoid mass projecting into the endometrial cavity, which was found in 23 cases. Four cases had pedunculated tumors and the remaining two had broad-based sessile masses. Twenty-eight tumors had an irregular surface that was papillary in 20 cases (Figure 1) and lobulated in eight; the remaining tumor had a smooth surface.

The tumor appeared isoechoic relative to myometrium in 16 cases, hypoechoic in 12 cases and hyperechoic in one. Occasionally the tumors had a trabecular appearance and all had a heterogeneous echotexture (Figure 2). Intratumoral clefts or fissure-like cystic areas were observed in 10 cases (Figure 3) and other ill-defined hypoechoic areas suggestive of necrosis or hemorrhage were seen in four and seven cases, respectively.

In the 24 cases examined, color Doppler sonography depicted moderate to marked vascularity in 20 cases, and this appeared as single or multiple irregular feeding vessels entering through the pedicle in 15 cases (Figure 4) or as randomly dispersed vessels in nine cases; RI values of these vessels ranged from 0.28 to 0.57 (mean, 0.41).

In 27 of the 29 cases, demarcation from underlying myometrium was poor, whereas in the remaining two cases tumors had a well-circumscribed margin. Myometrial invasion was observed in 27 cases; 11

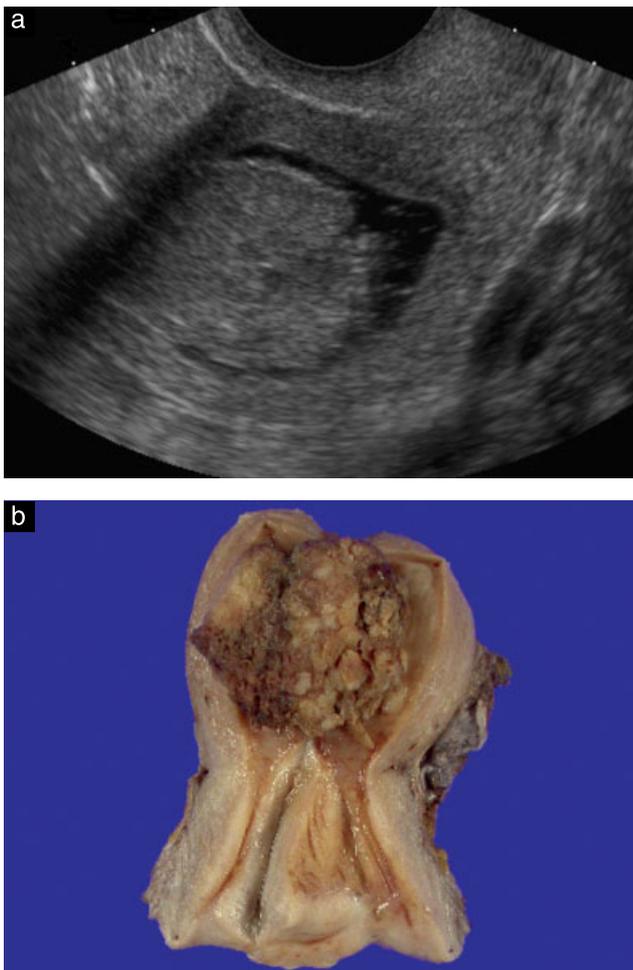


Figure 1 Malignant mixed Müllerian tumor in a 53-year-old woman. (a) Sagittal saline contrast sonohysterographic image of the uterus showing a polypoid endometrial mass (3.0×2.6 cm) with a papillary surface projecting into the endometrial cavity in the fundus. (b) Hysterectomy specimen showing a fungating tumor arising from the fundus and filling the uterine cavity, with lobulations and characteristic leaf-like projections on the external surface.

cases showed superficial invasion and 16 deep invasion. On pathological examination, myometrial invasion was present in 28 cases, of which 12 cases were superficial and 16 were deep; the depth of myometrial invasion was underestimated on ultrasound in four cases and overestimated in three.

As for other sonographic findings, dilatation of the endometrial cavity with fluid was observed in 11 cases. Cervical invasion was present in five cases and adnexal invasion with a mass in the ovary and/or tube was present in 10 cases; these findings correlated well with the gross and histological findings. Three cases had fluid in the cul-de-sac and five had masses on the pelvic peritoneal surface. In eight cases, the cytological results of peritoneal washing revealed pelvic peritoneal metastases.

DISCUSSION

Uterine MMMTs arise from the endometrium, most commonly in the uterine fundus, but rare tumors may

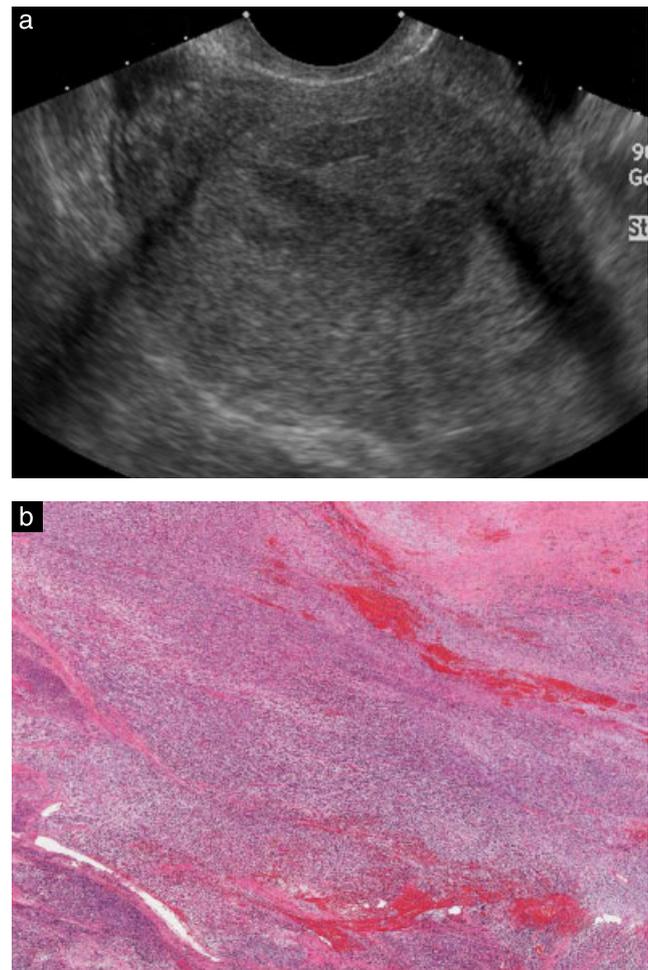


Figure 2 Malignant mixed Müllerian tumor (MMMT) in a 47-year-old woman. (a) Transverse transvaginal sonographic image of the uterus showing a heterogeneously hypoechoic mass (5.0×4.2 cm) with a trabecular appearance and interspersed hyperechoic areas. (b) Photomicrograph (original magnification, $\times 40$) of the resected tumor showing a biphasic pattern featuring both a well-differentiated endometrioid adenocarcinoma and a malignant stroma with rhabdomyosarcomatous differentiation in the center, consistent with MMMT. The sarcomatous part of the tumor is arranged in a trabecular pattern by interlacing spindle-cell fascicles that correspond to the hypoechoic area with a trabecular appearance on ultrasound.

arise in the uterine cervix. This type of tumor is typically a large fungating mass that usually fills the uterine cavity and occasionally prolapses through the cervical os. Its cut surface is usually fleshy with blunt polypoid projections on the external surface, which often show areas of hemorrhage, necrosis and cystic changes. Myometrial invasion is frequently observed. The tumor extends to the endocervix in 25% of cases^{1–3}. Definitive diagnosis of the disease is usually made by performing curettage, but it is often difficult to make a specific preoperative diagnosis because, in most cases, an endometrial biopsy can indicate either carcinoma or sarcoma. Preoperative radiological diagnosis is somewhat limited by the rarity of MMMTs, and the lack of specific imaging findings prevent distinguishing them from other malignant tumors of the uterine corpus⁷.

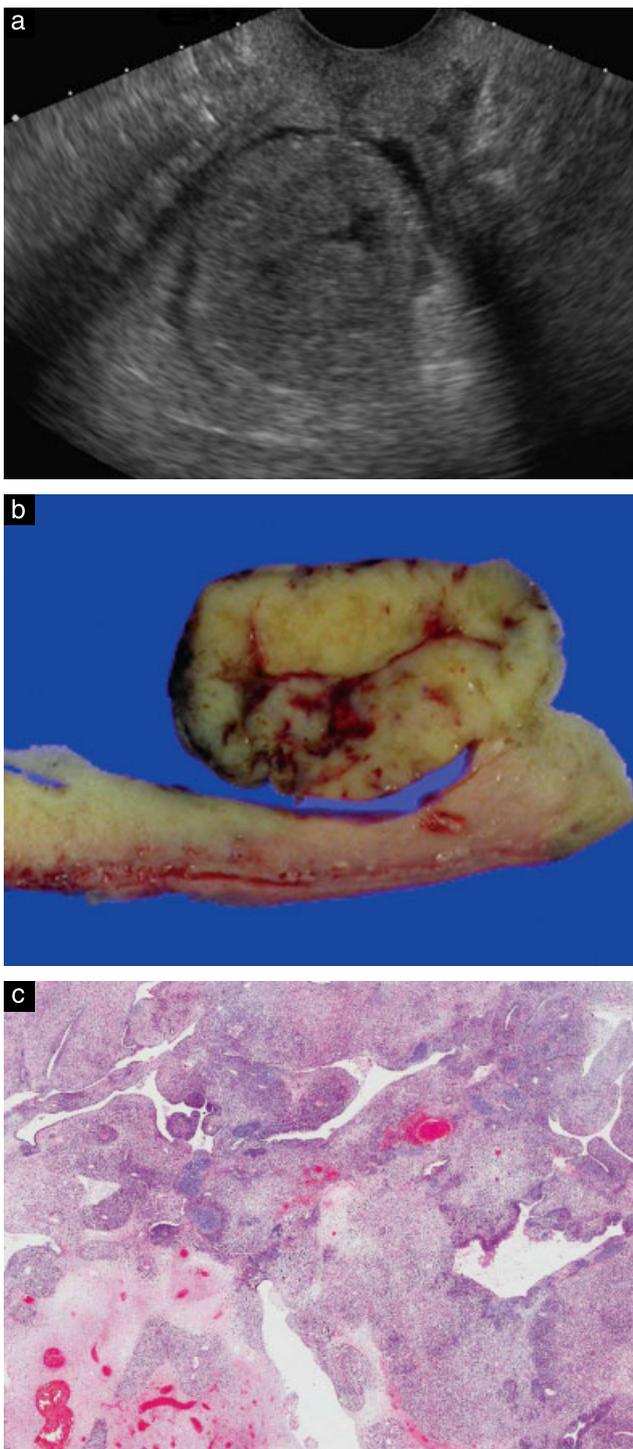


Figure 3 Malignant mixed Müllerian tumor in a 69-year-old woman. (a) Transverse saline contrast sonohysterographic image showing a polypoid mass (4.2 × 3.5 cm) with a well-defined cleft-containing or fissure-like cystic area in the posterior corpus. (b) Cut section of the resected tumor showing central, broad or branching clefts measuring 0.3–1.0 cm. (c) Photomicrograph (original magnification, × 10) showing polypoid or leaf-like protrusions of sarcomatous stroma displaying cartilaginous differentiation into cystically dilated malignant glands.

The sonographic findings of these tumors have rarely been reported in the literature. In a few case reports, their transvaginal sonographic appearance has been

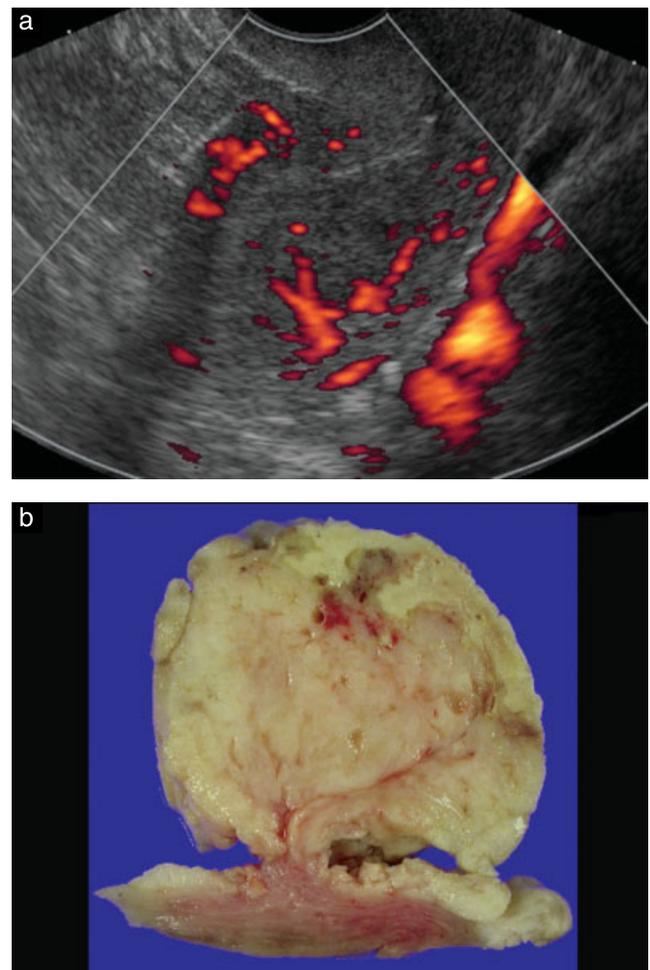


Figure 4 Malignant mixed Müllerian tumor in a 57-year-old woman. (a) Sagittal color Doppler image of the uterus showing a single feeding vessel at the base of the tumor. (b) Cut surface of the resected tumor showing a large feeding vessel, which entered through the pedicle, and branching small vessels within the mass.

variably described as a large intracavitary mass with expansion of the endometrial cavity and myometrial invasion or as a bulky mass replacing the entire uterus with a contiguous extrauterine mass in the adnexa and cul-de-sac^{7–11}. Two patterns of sonographic appearance have been previously identified in cases of uterine MMT, with the tumor presenting as either an intracavitary polypoid mass or a diffuse mass replacing the uterus^{8–10}. In addition, a homogeneous echogenic minimal diffuse thickening of the endometrium has been described as a less common presentation^{6,8}, and a pedunculated lesion protruding into the endocervical canal has also been described¹². A recent case of MMT arising from an endometrial polyp presented as a heterogeneous, thickened well-defined endometrium with some cystic areas and the myometrial–endometrial interface was well defined¹⁴. Another case of a tamoxifen-induced MMT that appeared as a small cavitory polyp has also been reported⁶. The majority of intracavitary masses so far described in the literature have been heterogeneous or hyperechoic, often with anechoic cystic areas or necrosis, and have in common

myometrial invasion and frequent extension into the endocervix^{8–11}.

A few case studies have reported the vascular features of MMMTs as assessed by Doppler sonography. These tumors typically show prominent vascularity, which appears as irregular thin and randomly dispersed vessels in either peripheral or central areas, or both, and low impedance¹², confirming previous findings in uterine sarcoma reported by Kurjak *et al.*¹³. However, another study reported that vascularization is mainly peripheral and tumor hypervascularity is not shown⁷. A more recent report described 3D power Doppler findings that showed a highly vascularized lesion with a main feeding vessel and abnormal branching patterns¹⁴.

In the present study, most tumors involved the uterine corpus and less commonly the fundus. Almost all tumor lesions in our cases were polypoid, which is consistent with previously reported findings⁸, and no diffuse mass lesion replaced the uterus. In addition, we found that growth of a pedunculated lesion into the endocervical canal was rare. With the exception of only one tumor with a smooth surface, tumor surfaces were irregular in all cases, and showed typical papillary contours that represented blunt polypoid, exophytic projections on the external surfaces on gross examination. The papillary nature of tumor surfaces, demonstrated in our cases of uterine MMMT, might be one of the characteristic imaging findings for these tumors.

Tumor echogenicities were mostly heterogeneously isoechoic or hypoechoic, often with a trabecular appearance, interspersed with hyperechoic areas. Histopathological examinations showed that these areas, hypoechoic to isoechoic by ultrasound, appeared to correspond to regions of predominantly sarcomatous tissue, which was arranged in a trabecular pattern with interlacing spindle-cell fascicles, whereas the areas of high echogenicity chiefly corresponded to carcinomatous tissue containing glandular structures. Previous case reports have described the hyperechogenicity and heterogeneous echotexture of this tumor. Whilst the latter was observed in the present study^{8–10}, we rarely observed a predominantly hyperechoic mass. The presence of clefts or fissure-like cystic areas revealed by ultrasound is the most distinctive difference between our findings and those of previous reports. Pathological examinations revealed these cystic areas to be endophytic protrusions of malignant stroma into cystically dilated glands lined by malignant epithelium; the appearances of intraglandular protrusions ranged from mound-like minor indentations to polypoid leaf-like protrusions. Ill-defined anechoic to hypoechoic intratumoral areas were also common and corresponded to areas of focal hemorrhage or necrosis as determined by gross and pathological examinations.

In the present study, MMMTs usually had feeding vessels, which typically entered through the pedicle, and contained small branching vessels, which were also evident on gross examination; these findings are compatible

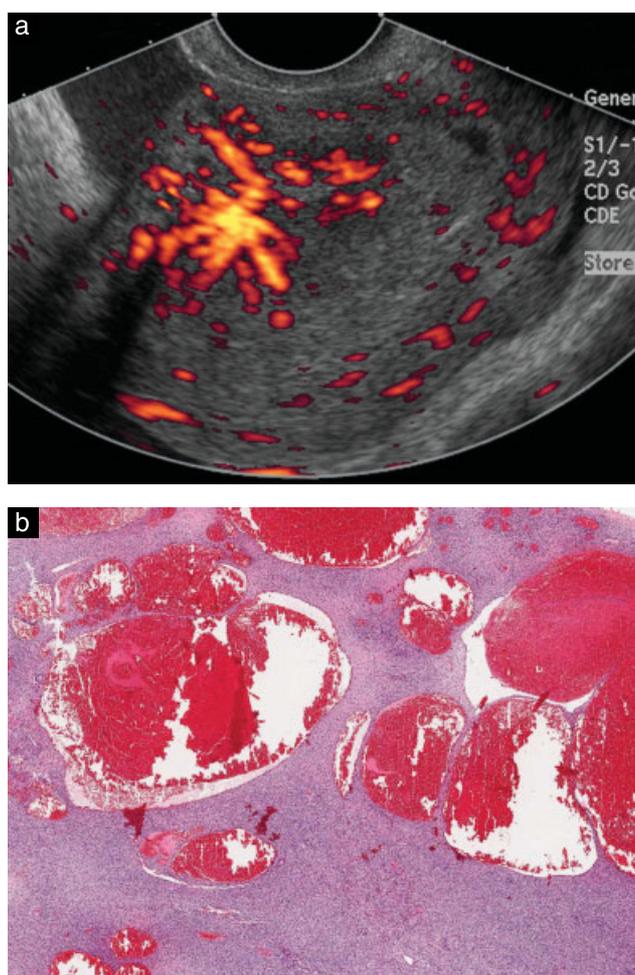


Figure 5 Malignant mixed Müllerian tumor in a 47-year-old woman. (a) Sagittal color Doppler image of the uterus showing multiple irregular feeding vessels and a marked vascularity in the hypoechoic solid area of the tumor, with a measured resistance index of 0.41 (not shown). (b) Photomicrograph (original magnification, $\times 40$) of the resected tumor showing multiple thick-walled large blood vessels in the sarcomatous stromal part of the tumor, consistent with the area of prominent vascularity on ultrasound.

with those of prior reports^{12–14}. Color Doppler sonography depicted marked vascularity in the hypoechoic solid areas of the tumors. We suggest that this prominent vascularity relates to the multiple thick-walled, large blood vessels in sarcomatous regions found during histologic examinations (Figure 5). However, these findings contradict an earlier observation of a higher degree of neovascularization in the epithelial than in the mesenchymal component¹². MMMTs usually exhibit a poorly defined margin with underlying myometrium and myometrial invasion. Invasion to the adnexa and pelvic peritoneal metastasis in the cul-de-sac also were found frequently. These findings are similar to those of previous reports^{8,9}. However, dilatation of the endometrial cavity and cervical invasion were relatively uncommon in our study.

In summary, we found that sonography revealed distinct features of uterine MMMTs that corresponded well with gross and microscopic pathological findings.

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