CASE REPORT AND LITERATURE REVIEW

Uterine Leiomyoma Variants: Case Reports and Literature Review

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Abstract

According to the World Health Organization (WHO) criteria for uterine smooth muscle, tumors have historically been distinct in benign leiomyomas, leiomyomas variants, and malignant leiomyosarcomas based on cytological atypia, mitotic rate, and presence or absence of tumor cell necrosis. Ultrasound, especially new techniques such as three-dimensional (3D)/four-dimensional (4D) ultrasound and 3D/4D color Doppler, is an excellent tool in the hands of ultrasonographers in the detection of atypical myomas and potential malignancy in uterine fibroids. Preoperative detection of malignancy in leiomyoma is a challenge for the ultrasonographer. It is very important to define an atypical leiomyoma by ultrasound examination because of its specificity, this type of leiomyoma can mimic leiomyosarcomas and can be precursors for the development of leiomyosarcoma.

Keywords: Ultrasound morphology, Uterine leiomyoma variants, Three-dimensional/Four-dimensional ultrasound, Three-dimensional power Doppler.

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Introduction

The morphologic features of uterine smooth muscle tumors include architecture, growth pattern, cellular characteristics, and constituents of the intercellular stroma. They are divided into benign leiomyoma and variants, uterine smooth muscle tumors of uncertain malignant potential (STUMP), and malignant leiomyosarcoma.

Uterine leiomyomas are the most common benign mesenchymal tumor derived from smooth muscle. In about 90% of cases, leiomyomas are of the conventional type, in some cases, leiomyomas accelerate in growth during pregnancy and involute with the onset of menopause.[1]

A smaller percentage is made up of leiomyoma variants, and this group includes "atypical myomas" that have a low risk of recurrence and is synonymous with benign tumors (leiomyoma with bizarre nuclei, symplastic leiomyoma, or pleomorphic leiomyoma), and mitotically active leiomyoma (cellular and highly cellular leiomyoma, epithelioid leiomyoma, and myxoid leiomyoma), each has distinctive hallmarks that enable subclassification.[2]

The risk of malignant transformation into leiomyosarcomas is rare, but leiomyosarcomas can arise *de novo*, without leiomyoma as a "base." According to the World Health Organization (WHO) (2003), uterine STUMP is a borderline tumor between benign leiomyoma and malignant leiomyosarcoma.[3]

Cellular Leiomyoma

Generally, these leiomyoma variants have a benign potential, and surgical treatment is sufficient, so postoperative adjuvant therapy and routine follow-up are not strictly recommended, but the possibility of recurrence cannot be excluded even though the chances are low.[4]

However, a recent study suggested that cellular leiomyomas exhibiting chromosome 1p deletions, a genetic alteration found in leiomyosarcoma, may be clinically more aggressive and require more intense surveillance.[5]

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Ultrasound

Ultrasound, especially new techniques such as three-dimensional (3D)/four-dimensional (4D) ultrasound and color Doppler, is an excellent tool in the hands of ultrasonographers in the detection of atypical myomas and potential malignancy in uterine fibroids.

There are certain characteristics that cellular myomas have, namely, they are singular and larger than leiomyomas and generally, there is no adenomyosis, unlike leiomyomas where adenomyosis is often an associated finding. The patient is symptomatic with menometrorrhagia, and the indication for the imaging study is "enlarging leiomyoma."[6]

Case 1

A 58-year-old patient, in menopause, comes for an examination due to abdominal discomfort from several months ago. She has given birth twice, both naturally. There are no concomitant diseases, he is not taking any therapy. Pulmonary alveolar proteinosis (PAP) is without pathology. A bimanual examination showed a generally enlarged free uterus.

Ultrasound examination according to Morphological Uterus Sonographic Assessment (MUSA) classification[7]: well-defined round lesion dimensioned 7 × 8 × 7 cm, edge shadowing (Fig. 1) localized in the intramural subserosal left lateral part of the uterus, mixed echogenicity (Fig. 2). On two-dimensional (2D) color Doppler ultrasound, rich vascularity of the lesion with the multifocal origin of the blood vessels, color score 3/4 (Fig. 3).[8] On 3D/4D color Doppler circumferential flow and intralesional rich vascularization is detected (Fig. 4).

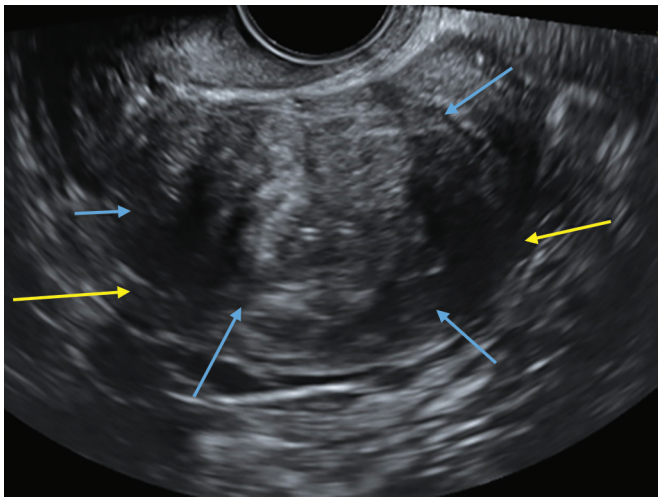

Fig. 1: Ultrasound finings of tumor mass on 2D ultrasound—well-defined round lesion (blue arrows) edge shadowing (yellow arrow), mixed echogenicity

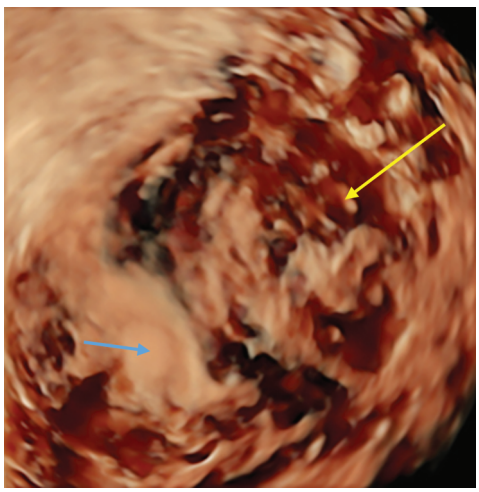

Fig. 2: Three-dimensional (3D)/4D ultrasound of the same lesion—localized in the intramural subserosal left lateral part of the uterus, mixed echogenicity

Treatment

After adequate preparation, surgical treatment was performed (total hysterectomy with oophorectomy). Microscopic findings and the final diagnosis were cellular leiomyomas of the uterus.

Leiomyoma with Bizarre Nuclei (Simplistic, Atypical Leiomyoma)

The leiomyoma with bizarre nuclei (simplistic, atypical leiomyoma) is a rare variant of uterine smooth muscle tumors

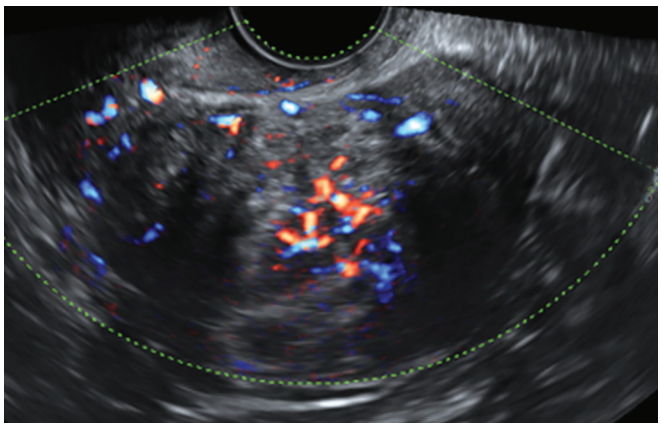

Fig. 3: Two-dimensional (2D) color Doppler ultrasound—rich vascularity of the lesion with the multifocal origin of the blood vessels, color score 3/4

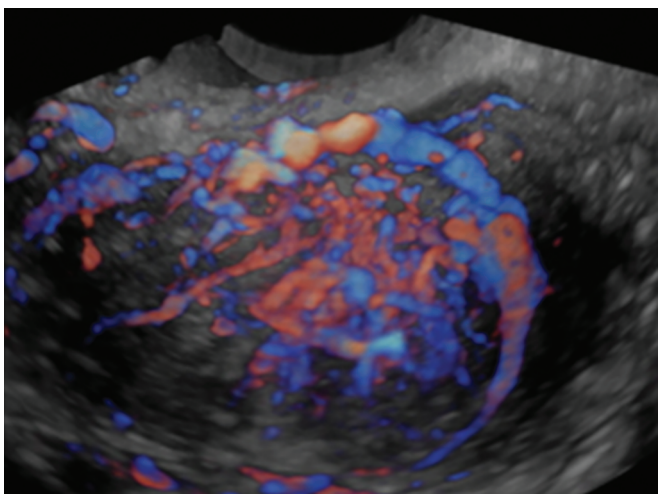

Fig. 4: Three-dimensional (3D)/4D color Doppler of the lesion—circumferential flow with intralesional rich vascularization

giving an incidence of 1% and a low rate of intra-abdominal and negligible risk for distant metastasis.[9]

The characteristics of atypical leiomyomas on 2D/3D ultrasound and magnetic resonance imagingare a solid tumor mass with cystic degeneration and homogeneous signal intensity.[10]

Ultrasound features of leiomyoma with bizarre nuclei (bizarre/symplastic/atypical leiomyoma), or mitotically active leiomyoma, cellular and highly cellular leiomyoma, dissecting leiomyoma, and leiomyoma with increased cellularity may have the same macroscopically pathological features as leiomyoma and may have increased vascularity, as this feature seems to be related to cellularity.[11]

Case 2

A 22-year-old patient, nulliparous with the main symptom of menometrorrhagia. She has given birth twice, both naturally. There are no concomitant diseases, she is not taking any medications. PAP is without pathology. A bimanual examination showed a generally enlarged free uterus.

Ultrasound examination according to MUSA classification[7]: well-defined round nonhomogeneous lesion dimensioned 5 × 4 × 3 cm, intratumoral multiple small cystic areas, edge shadowing localized full intramural of the myometrium. (Figs 5 and 6) On 2D color Doppler ultrasound, rich vascularity of the lesion with the multifocal origin of the blood vessels, a color score of 3/4[8] (Fig. 7). On 3D/4D rich vascularization color Doppler location of vessels: circumferential, intralesional, nonuniform. Vessel morphology: multiple, large, and small unequal vessels (Fig. 8).

Treatment

After adequate preparation, surgical treatment was performed (myomectomy).

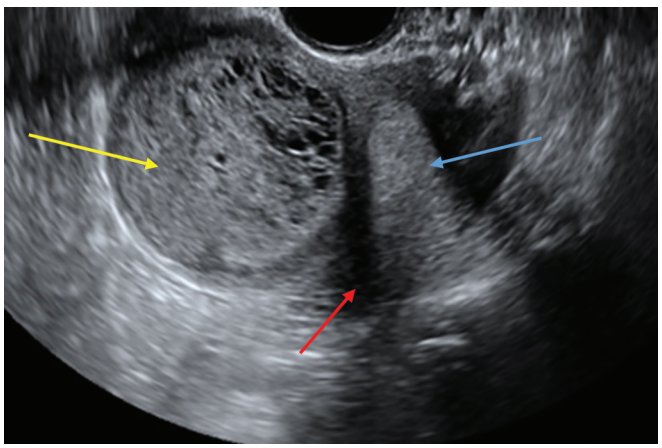

Fig. 5: Two-dimensional (2D) ultrasound—well-defined round nonhomogenous lesion dimensioned 5 × 4 × 3 cm, (yellow arrow); intratumoral edge shadowing localized full intramural of the myometrium, (red arrow); endometrium (blue arrow)

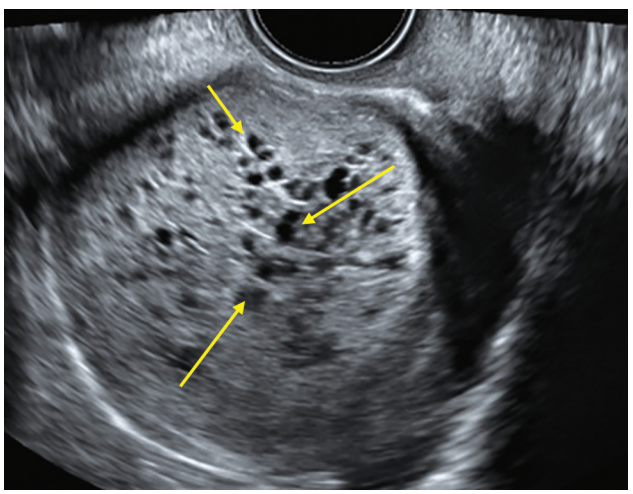

Fig. 6: Two-dimensional (2D) ultrasound—multiple small cystic areas (yellow arrow)

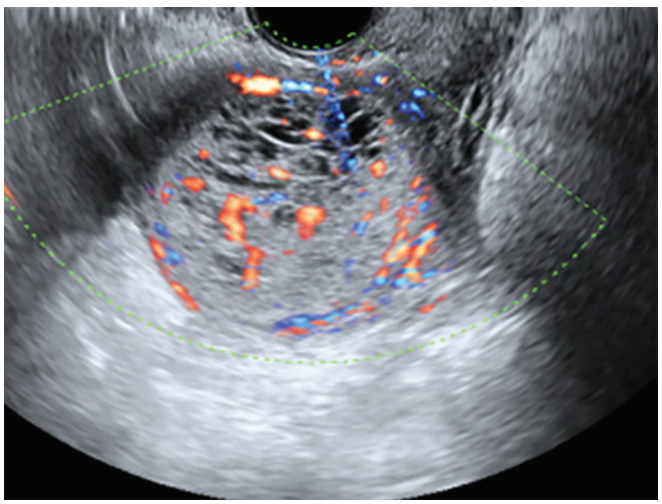

Fig. 7: On 2D color Doppler ultrasound, rich vascularity of the lesion with multifocal origin of the blood vessels, color score 3/4

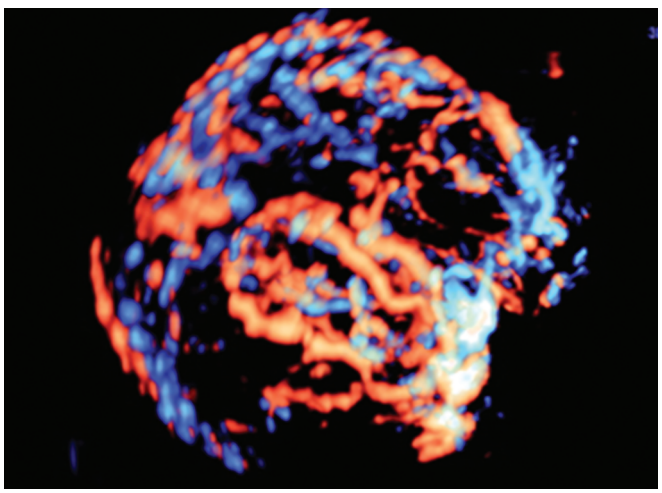

Fig. 8: On 3D/4D rich vascularization; color Doppler location of vessels—circumferential, intralesional, nonuniform. Vessel morphology—multiple, large, and small unequal vessels

Microscopic findings and the final diagnosis were leiomyomas with bizarre nuclei (simplistic, atypical leiomyoma). The patient's follow-up just started.

Uterine STUMP

Smooth muscle tumors of uncertain malignant potential (STUMP) is a borderline tumors between benign leiomyoma and malignant leiomyosarcoma[3] and can be found in women in their mid-40s who had a preoperative diagnosis of myoma as a postoperative pathohistological finding. The clinical signs and symptoms like pelvic pain, abnormal uterine bleeding (menometrorrhagia), and pelvic discomfort are the same as leiomyoma and leiomyosarcoma. Risk factors and prognosis are not fully understood, but in long-term follow-up, there is a potential for recurrence or metastasis.[3]

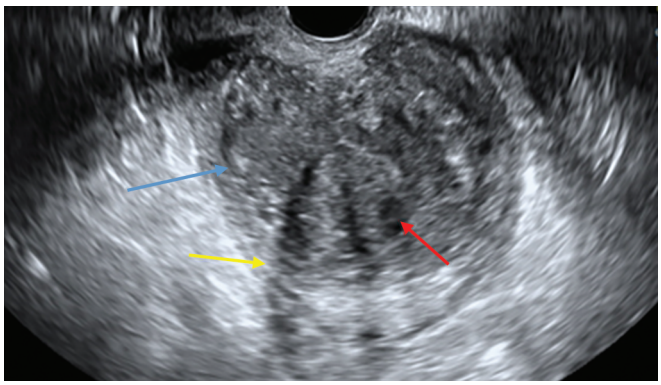

Fig. 9: Two-dimensional (2D) ultrasound—intramural localization of the tumor (blue arrow), ill-defined margins of the tumor mixed echogenicity, heterogeneous appearance, small cystic forms (red arrow), present acoustic shadowing, no free fluid (yellow arrow)

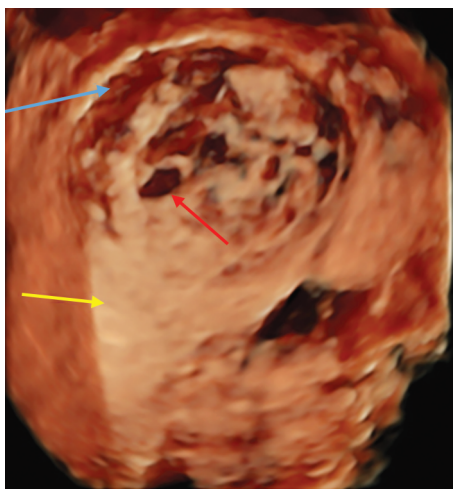

Fig. 10: Three-dimensional (3D) ultrasound—Ill-defined margins of the tumor, mixed echogenicity, (blue arrow) heterogeneous appearance, small cystic forms (red arrow), endometrium (yellow arrow)

Imaging Findings of STUMP

Preoperative STUMP diagnosis or differentiation from leiomyoma–leiomyosarcoma with imaging modalities is not easy. Because of their rareness uterine STUMPs have been only sporadically described in the imaging literature. Generally, STUMPs are located in the corpus, but they can occur in the broad ligament, ovaries, cervix, or vaginal canal.[12]

The sonographic findings associated with STUMP generally showed a single well-defined tumor mass, hyperechoic, heterogenous, noncystic, 50% calcification, acoustic shadowing, and presence of free fluid.[13,14]

Case 3

A 41-year-old, gravida V, parity III, woman, premenopausal state, complaint of menometrorrhagia. She had no systemic disease and no other history of surgical procedures.

According to MUSA and International Endometrial Tumor Analysis classification consensus,[7,14] sonographic findings of the tumor are—2D/3D ultrasound: Number of tumors 1, a diameter of the tumor 15 cm, intramural localization of the tumor, ill-defined margins of the tumor, mixed echogenicity, heterogenous appearance, small cystic forms, present acoustic shadowing, no free fluid. 2D/3D color Doppler—nonuniform vascularity, color score 3,[8] intralesional location of vessels. Vessel morphology: multiple; unequal size, irregular branching (Figs 9 to 12).

Treatment

After adequate preparation, surgical treatment was performed (total hysterectomy with oophorectomy). Pathohistological analysis on the macro-preparation showed that the tumor is multinodular, whitish in color in cross-section, with an elastic, firm consistency. There is no necrosis or hemorrhage in the tumor tissue. Microscopic findings and the final diagnosis indicate STUMP. The patient's follow-up is in progress.

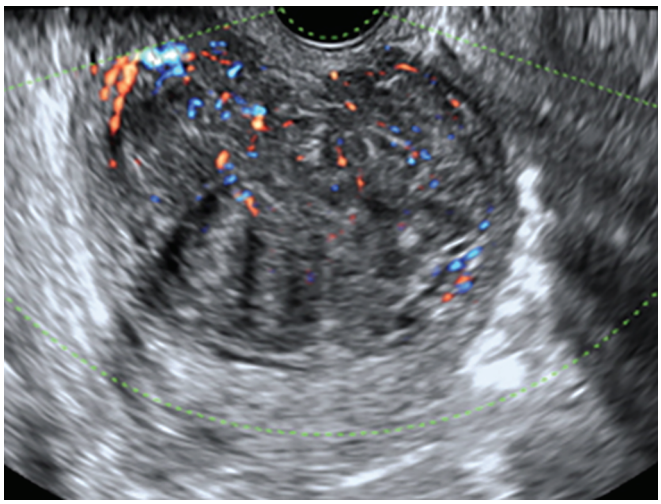

Fig. 11: Two-dimensional (2D) color Doppler—nonuniform vascularity, color score 3, intralesional location of vessels

Case 4

A 50-year-old, gravida II, parity II, woman, in a perimenopause state, complained of abdominal discomfort and vaginal bleeding. Sonographic findings: 2D/3D ultrasound—number of tumors 1, a diameter of the tumor 12 cm, subserous intramural localization of the tumor localized on the uterine fundus, well-defined margins of the tumor, echogenicity—heterogeneous appearance, no present acoustic shadowing, no free fluid. 2D/3D color Doppler: nonuniform vascularity on the base, no color signal detection in the tumor, color score 0, and no intralesional location of vessels (Figs 13 to 16).

Treatment

After adequate preparation, a total hysterectomy with adnexectomy was performed on the patient. Pathohistology—the nodule is dark red in color, soft in consistency, with a shiny cross-sectional surface, clearly demarcated toward the surrounding myometrium. Extensive necrosis and

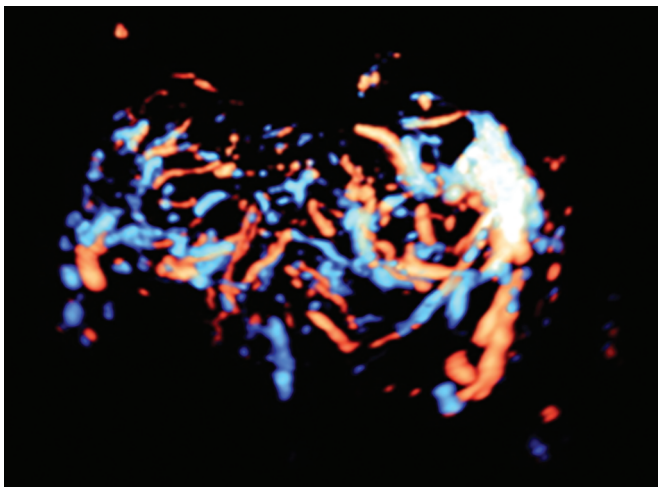

Fig. 12: Three-dimensional (3D)/4D color Doppler—vessel morphology: multiple; unequal size, irregular branching, no strong circumferential vascularization visible

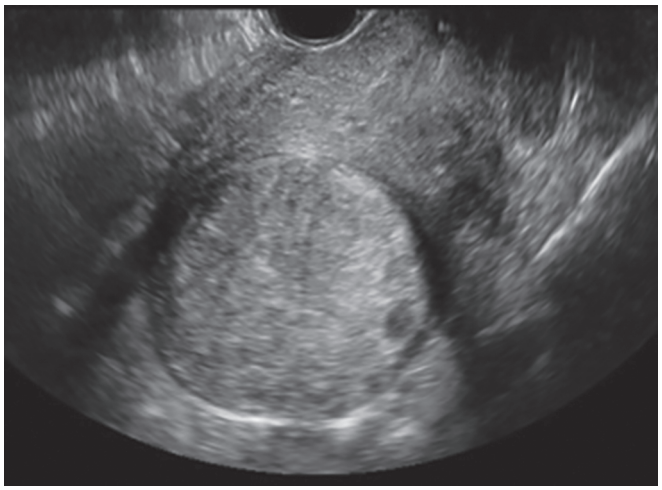

Fig. 13: Two-dimensional (2D) ultrasound—single tumor with subserous-intramural localization of the tumor on the uterine fundus, well-defined margins, heterogeneous appearance, no present acoustic shadowing, no free fluid

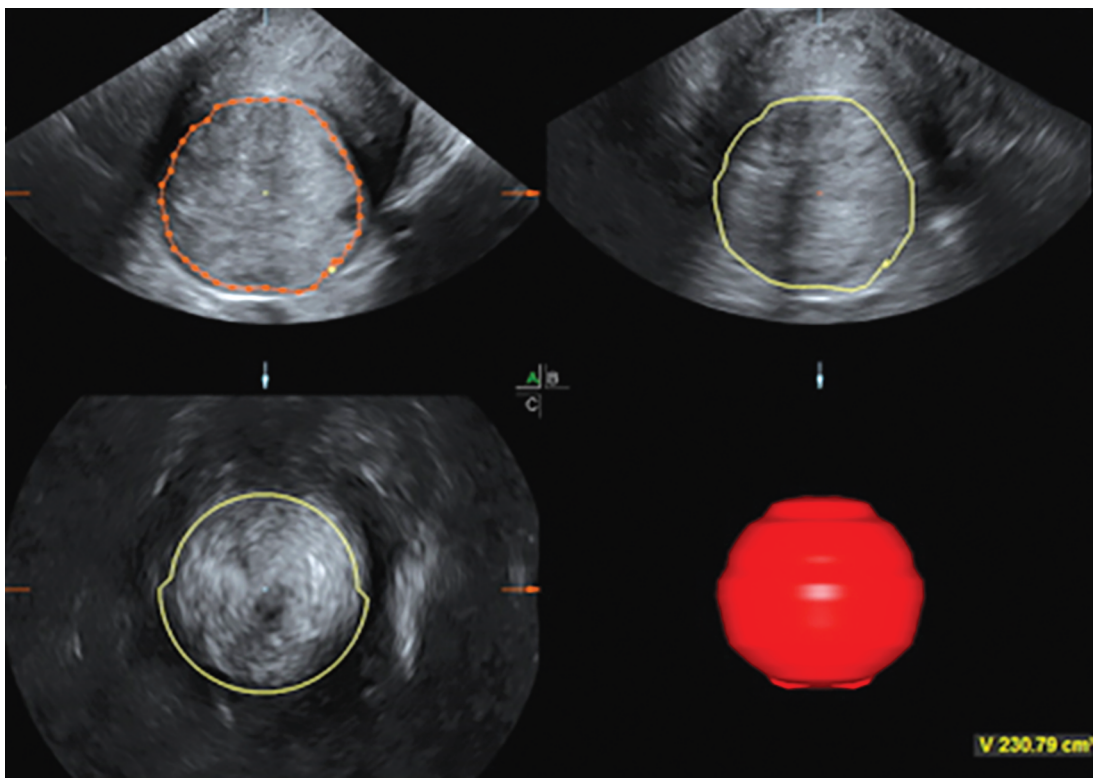

Fig. 14: Vocal measurement of the tumor mass showed a large volume of the tumor

hemorrhage in the tumor are detected at the cross-section. Microscopic findings and the final diagnosis indicate STUMP. The patient's follow-up is in progress.

Preoperative diagnosis of STUMP is very difficult, so postoperative pathohistological findings are the most frequent confirmation of STUMP. If the tumor does not meet the criteria for leiomyosarcoma and has a combination of Stanford's criteria, the STUMP diagnosis is accurate. The reported recurrence rate for STUMP is 7–27%. Tumor necrosis, degree of atypia, and mitosis are correlated with malignant behavior, but the relationship with recurrence is not clear.[15,16]

Smooth muscle tumors of uncertain malignant potential (STUMP) and leiomyosarcoma behave differently in relation to tumor growth and recurrence, therefore it is very important to make a differential diagnosis of these two tumors. Leiomyosarcoma is a tumor that behaves very aggressively and quickly gives recurrence of the disease, unlike STUMP, which does not grow so quickly, and generally, if the recurrence of the disease occurs, it is after a period of a few years.[17]

As for adjuvant therapy, progesterone, GnRH analog or chemotherapeutic agents are available. Unfortunately, none of these established adjuvant therapies, at least so far, have significant evidence in preventing disease recurrence. If the efficacy of progesterone is confirmed, a progesterone-releasing intrauterine device (LNS-IUS) may be a valid option in the event of fertility-sparing surgery.[18]

Uterine Leiomyosarcoma

Uterine leiomyosarcoma is a malignant tumor with a poor prognosis. The incidence of this tumor is 3–7% of all uterine cancers. Preoperative diagnosis of leiomyosarcoma is difficult, primarily because leiomyosarcoma is rare so about 0.1–0.4% of operative material that is detected preoperatively as a leiomyoma pathology leads to the diagnosis of Leiomyosarcoma. The rapid growth of leiomyomata in menopause carries the risk of leiomyosarcoma.[19,20]

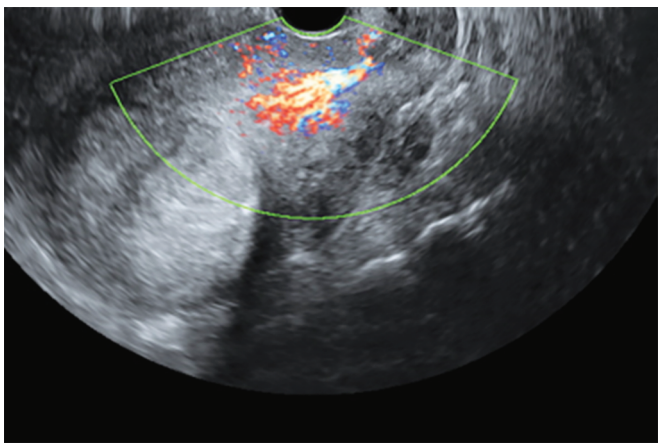

Fig. 15: Three-dimensional (3D)color Doppler—nonuniform vascularity on the base no color signal detection in the tumor, color score 0, no intralesional location of vessels

Ultrasound Findings of Leiomyosarcoma

On ultrasound, leiomyosarcomas have the appearance of a large solid tumor mass (>5 cm), which has heterogeneous echogenicity due to secondary cystic degeneration of the tumor mass. Internal shadows or fan-shaped shadowing, which is detected in leiomyoma and adenomyosis, are rarely detected in leiomyosarcoma. 2D/3D color Doppler has an image of a tumor with increased vascularity, rich circumferential vascularity on the periphery of the tumor, but also rich central vascularity of the tumor, which is a sign of suspicion that the tumor is leiomyosarcoma.[7,21,22] New angiogenesis detected by color Doppler measurement of the resistance index (RI) may be a useful diagnostic tool according to RI cut-off values below 0.4.[21]

Case 5

A 42-year-old, gravida II, parity II, with hypermenorrhea, complaint of abdominal discomfort, and anemia. The patient does not provide anamnestic information about previous surgical procedures.

The bimanual examination showed an enlarged free uterus with a nonregular outline.

- Sonographic findings: 2D/3D ultrasound: Number of tumors 4, a diameter of the tumors between 2 × 3 × 2 cm smallest (Fig. 17) to 5 × 6 × 5 cm biggest one (Fig. 18), subserous-intramural localization of the tumors, the tumors with well-defined margins, heterogeneous echogenicity, free margins of the endometrium, present acoustic shadowing on tumors except for the biggest one, no free fluid (Figs 17 to 19).
- 2D/3D color Doppler: Nonuniform vascularity, color score 4 on the suspected malignant tumor, circumferential flow but also the rich intralesional central location of vessels.
- Vessel morphology: Multiple; unequal size, irregular branching[21,22] (Fig. 20).
- Treatment: After adequate preparation, a total hysterectomy without adnexectomy was performed on

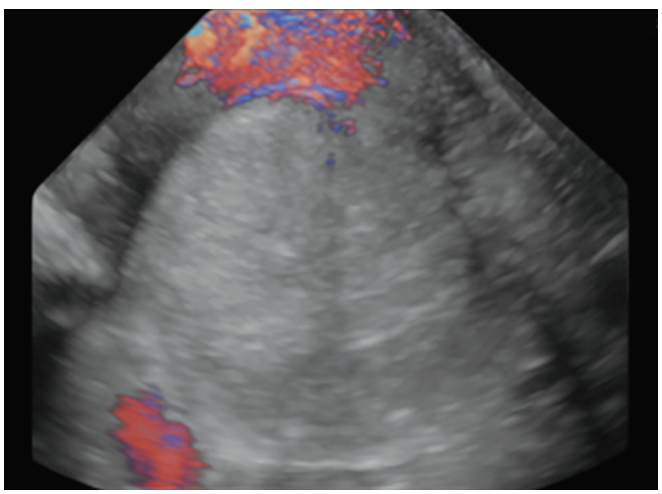

Fig. 16: Same situation at transversal plane—no intratumoral vascularization

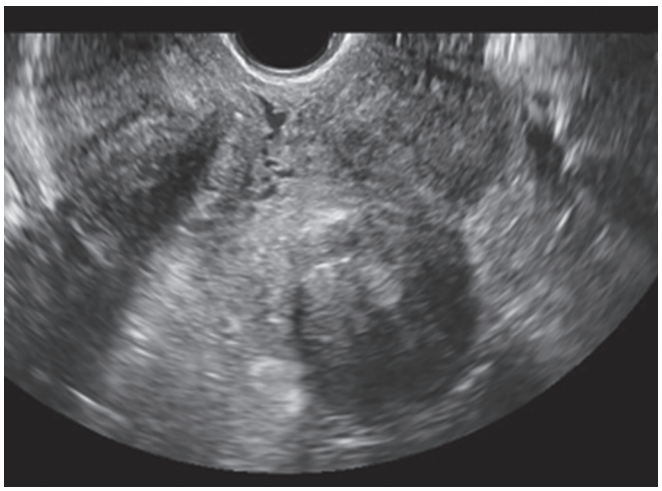

Fig. 17: Two-dimensional (2D) ultrasound of existing leiomyomas—subserous-intramural localization of the tumors, well-defined margins of the tumors, heterogeneous appearance, present acoustic shadowing on tumors

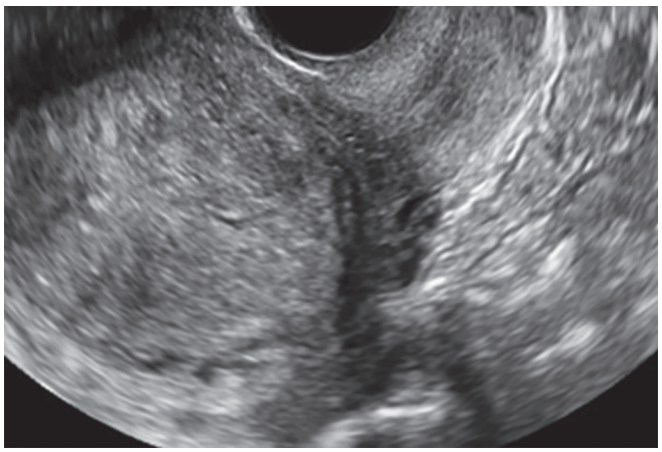

Fig. 18: Two-dimensional (2D) ultrasound of the biggest tumor—intramural localization of the tumor, well-defined margins, heterogeneous appearance, no present acoustic shadowing on the tumor.

the patient. Histopathological findings were in addition to leiomyoma, but the largest tumor is leiomyosarcoma of the uterus.

Conclusion

Preoperative detection of atypical forms and malignancy in leiomyoma is a challenge for the ultrasonographer. It is very important to define an atypical leiomyoma by ultrasound examination because of its specificity, this type of leiomyoma can mimic leiomyosarcomas and can be precursors for the development of leiomyosarcoma. Women who are of reproductive age and plan to have children belong to the group where the minimally offensive operative approach is important in terms of preserving the fertile potential. On the other hand, even with minimally aggressive treatment (myomectomy) in

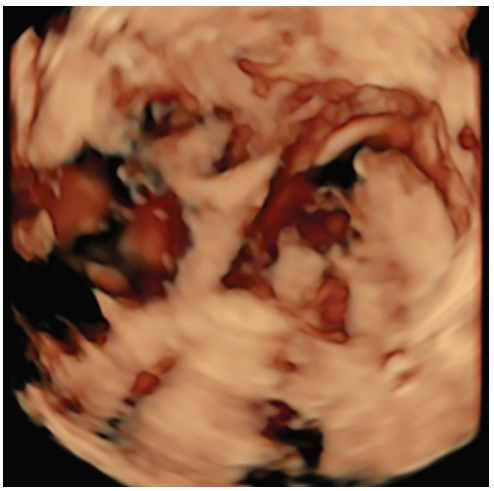

Fig. 19: Three-dimensional (3D)/4D ultrasound—free margins of the endometrium

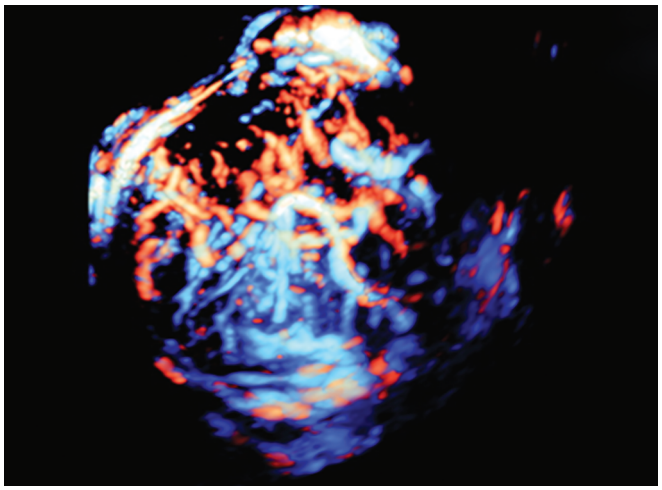

Fig. 20: 3D/4D Color Doppler—nonuniform vascularity, color score 4, circumferential flow but also the rich central intralesional location of vessels. Vessel morphology: multiple; unequal size, irregular branching

some variants of uterine fibroids, postoperative monitoring is important because the possibility of recurrence of atypical leiomyoma is still unknown. Ultrasound, especially new techniques such as 3D/4D ultrasound and color Doppler, give an excellent visualization of the changes caused by malignancy, and this really allows us to preoperatively reduce the possibility of misdiagnosis of malignant myomas, and thus choose the right operative approach.

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