The Diagnostic Value of Multi-Modal Ultrasound on the Ovarian Serous Surface Papillary Borderline Tumor

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Research Article

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Abstract

Background: Compared with epithelial ovarian cancer, borderline ovarian tumor has earlier onset age and better prognosis. Ovarian serous surface papillary borderline tumor (SSPBT) is a special subtype of ovarian serous borderline tumor, which is rare in clinic. It is easy to be misdiagnosed as malignant before operation. SSPBT usually occurs in women of childbearing age. The operation of preserving fertility can have a higher pregnancy rate. Therefore, preoperative ultrasound for qualitative diagnosis of SSPBT is of great significance in the selection of surgical methods and treatment. There are few reports on the imaging of SSPBT, and the multimodal ultrasound features of SSPBT combined with conventional ultrasound, two-dimensional and three-dimensional contrast-enhanced ultrasound have not been reported. The purpose of this article is to explore the multimodal ultrasonic characteristics of ovarian SSPBT, combining its clinical and pathological features.

Result: The conventional ultrasound of ovarian SSPBT was characterized by large patchy substantial masses wrapped around the ovary.Large flaky dense fine anechoic areas could be seen in the parenchyma,accompanied by speckle strong echo with different degrees.Peritoneal implants were observed in 3 cases(60%)and ascites were found in 4 cases(80%).On further contrast-enhanced ultrasonography,with reference to the myometrium,the tumor on 2D-CEUS showed synchronous or delayed eccentric and inhomogeneous enhancement,and subsided earlier than the uterine wall.The tortuously running tumor trophoblast vessels from the periovarian of the affected side could be further observed clearly and stereospecially on 3D-CEUS.Angiographic rising time(RT),time to peak(TTP),peak intensity(PI),area under the curve(AUC)and half time of descending peak intensity(HT)were significantly different from those of the myometrium($P<0.05$).The speckled strong echo observed by conventional ultrasound was correlated with the sand body of the fiber stalk axis in the papillary structure under pathological microscope,while the tortuosity and dilation of microvessels in the fibrous connective tissue axis was the pathological basis of their CEUS perfusion.

Conclusion: There are characteristic manifestations of ovarian SSPBT on multimodal ultrasound,which are closely related to the pathological structure.Multimodal ultrasound has important reference value in the diagnosis of ovarian SSPBT.

1. Introduction

The incidence of borderline ovarian tumors (BOTs) accounts for about 15%~20% of epithelial ovarian tumors[1]. Its histological characteristics were defined as atypical hyperplasia of the epithelial ovarian cells without destructive stromal infiltration [2]. Compared with epithelial ovarian cancer, it occurs 10 to 15 years earlier and even with celiac spread or lymph node involvement, its prognosis is significantly better with 5-year and 10-year survival rates reported to be 95% and 85%, respectively[1, 3, 4]. Serous borderline tumor (SBT) is the most common type of BOTs, in which,the pathomorphologic features, biological behavior and prognosis are between benign serous tumor and low grade serous carcinoma. SSPBT is a special subtype of SBT, which is rare clinically, so previous reports are usually limited to individual

cases[5]. It is easy to be misdiagnosed as malignant preoperatively, and confirmed by postoperative pathology, due to its large solid mass, often accompanied by peritoneal diffusion or lymph node involvement and production of ascites. In addition, SSPBT tends to occur in women of childbearing age. For young patients with fertility requirements, fertility preserving surgery can be used, and a higher pregnancy rate could be achieved[6].Therefore, the qualitative diagnosis of SSPBT by preoperative ultrasound is of great significance in the selection of surgical methods and treatment plans.

The occurrence and metastasis of tumors are closely related to the formation of tumor blood vessels, and abnormal blood perfusion often occurs in tumors [7].CEUS that has been gradually applied to the ultrasound perfusion imaging of ovarian masses in recent years is a non-invasive imaging method. By using microvesicles similar in diameter to red blood cells, which can produce strong backscattering signals within tumor microvascular under the low mechanical index, real-time dynamically tumor microvascular perfusion can be obtained to improve the qualitative diagnosis of ovarian tumors and quantitative evaluation, that overcome the limitations of not being able to show slow blood flow using the color doppler flow imaging (CDFI)[7, 8]. 2D-CEUS can display the perfusion behavior of the lesion in the region of interest at a single level, while 3D-CEUS which combines CEUS with 3D imaging technology can further display the overall perfusion of the tumor in a stereoscopic, intuitive and continuous manner[9]. There are few imaging reports on SSPBT, and the characteristics of SSPBT under multimodal ultrasound combined with conventional ultrasound, 2D-CEUS and 3D-CEUS have not been reported. In this study, 5 cases of SSPBT confirmed by pathology in our hospital were retrospectively analyzed, and the diagnostic value of multimodal ultrasound on SSPBT will be discussed,combined with their clinicopathological characteristics.

2. Method And Materials

2.1 Clinical data collection

35 cases of ovarian serous borderline tumors confirmed by pathology were admitted and treated in our hospital, including 5 cases of SSPBT of the ovary, with an average age of 33 years (age range 22–43 years) from June 2010 to December 2019. All the 5 cases of SSPBT underwent ovarian tumor markers testing including carcinoembryonic antigen (CEA), carbohydrate antigen 19 – 9(CA199) and carbohydrate antigen 125(CA125),and conventional ultrasound examination before operation, among which 4 cases underwent further contrast-enhanced ultrasound. Postoperative pathologic sections of the tumor were reassessed by two pathologists and the international Federation of Obstetrics and Gynecology Surgery (FIGO) staging of the lesion was determined[10]. This study was approved by the institutional ethics committee of The First Affiliated Hospital of Fujian Medical University, and the informed consent was signed by all participants.

2.2 Ultrasonic instruments and methods

2.2.1 Routine ultrasonic scanning

The equipment routinely used in the study was an IU22 US system (Philips Medical Systems, Bothell, WA, USA) with a convex array probe(C5-1, 1–5 MHz)and an intracavitary probe (3D9-3v, 3-9MHz).The pelvic viscera were examined by routine abdominal and vaginal scanning to observe the location, size, echo and blood supply of the uterus and bilateral ovaries. If abnormal masses are found,their location, size, echo and blood supply were observed and attention was paid to their relationship with the ovaries, mass diffusion in the pelvis and peritoneum, and abdominal pelvic effusion.Subjective semi-quantitative evaluation of tumor blood supply was conducted according to the International Ovarian tumor Analysis (IOTA) rules (1 point: no blood flow signal; 2 points: only a small amount of blood flow was detected; 3 points: moderate amount of blood flow; 4 points: abundant blood flow signal) [11]

2.2.2 CEUS

Sonovue (BRACCO company, Italy) was used as contrast medium. The suspension was made by dissolving and diluting with 5ml saline solution and shaking. None of the 4 patients had severe renal insufficiency, pulmonary insufficiency, or cardiac insufficiency. In compliance with ethical factors, they signed an informed consent form for CEUS examination and 1.5 ml sonovue suspension was injected through the central cubital vein by mass injection, followed by rapid injection of 5 ml normal saline into the tube. The probe position was fixed and placed into the imaging state when the optimal tumor section was selected, and the uterine section was taken as a reference. Contrast agent was injected and contrast-enhanced ultrasound timer was started at the same time to continuously observe the contrast process of tumor and retain dynamic images. Observe the perfusion characteristics of the mass until the contrast agent was completely dissipated. Enhanced ultrasound examination would take at least 5 minutes. The quantitative analysis software of QLAB image processing software (Netherlands Philips Health-care version 9.1) was used to study several functional features relating to tumor blood perfusion. A contrast time-intensity curve (TIC) of lesions was automatically generated and analyzed and the relevant angiographic parameters (RT,TTP,PI,AUC and HT)were recorded separately.

3D-CEUS

After the contrast agent was completely cleared, the sampling frame size and scanning Angle(85 degrees) in the area of interest were adjusted. The abdominal 3D volume probe was enabled to entered the 3d imaging mode and 1.2ml acoustic contrast agent was injected intravenously in the same way during 2D-CEUS to observe the angiography process of the tumor. The 3D angiography images were repeatedly collected and stored from the arterial phase for 2–3 min. The Qlab software built in the instrument was used for image processing and analysis.

The sonographic characteristics of the tumor were assessed by two experienced sonographers by consensus.

2.3 Statistical Analysis

The statistical analyses were performed by using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Enumeration data were expressed as percentages, while measurement data were summarized as the

means ± SD. Paired T test was used for mean comparison, in which a difference of 0.05 was statistically significant.

3. Results

3.1 Conventional ultrasonic characteristics

All the 5 cases received conventional ultrasound examination, of which 4 cases (80%) showed unilateral or bilateral adnexal masses, and 1 case (20%) of pregnant at 38 weeks was missed diagnose. No obvious abnormal sonograms were found in the liver, gallbladder, pancreas and kidney ultrasound examination for the 5 cases.

The maximum diameter of 6 ovarian tumors in the 4 patients was about 132mm(mean, 83.3 ± 14.6mm), and all of them showed an irregular solid echo mass close to or wrapped around the ipsilateral ovary without obvious envelop, in which normal ovaries with small follicles could be seen (Fig. 1a-b, Fig. 2a-b).Many dense small anechoic areas that accompanied by short line strong echo in the back wall of 5 mass could be seen, which presented a fine grid. Speckled strong echoes in the clusters to different degrees were observed and in typical cases, numerous dotted strong echo were mixed with dense small anechoic areas, showing the sign of snowstorm (Fig. 2a);One mass presented isoechogenicity, with only a small area of dense small anechoic area, and no obvious dotted strong echo were observed. 3 cases (60%) showed multiple implantable nodule sonograms in the place such as surface of the uteru,retroperitoneum, greater omentum(Figure 1c, 2a). Minimal to moderate ascites were observed in 4 cases (80%).

Mild or moderate blood flow signals were observed in the 6 masses, in which the peak velocity of systolic blood flow ranged from 8.87cm/s to14.8cm/s(mean,11.1 ± 1.0cm/s), the blood flow resistance index (RI)O.42 to 0.57(mean,0.50 ± 0.03), and the IOTA score 2 ~ 3 points.

3.2 Features of contrast-enhanced ultrasound

Further 2D-CEUS and 3D-CEUS were performed for 6 ovarian tumors in 4 cases.Taking the myometrium as the contrast reference, the main nutrient vessels of the tumor originated from the periphery of the ipsilateral ovary, showing several radial large irregular branches. The tumors were enhanced from 11s to 14s, in which 4 lesions (66.7%) began to increase later than the uterine wall(Fig. 1d, 1f), and 2 lesions (33.3%) were enhanced synchronously(Fig. 2c, 2e). The enhancement pattern of the tumors showed low enhancement of eccentric inhomogeneity, and the regression time was earlier than the myometrium(Fig. 1e, 1f, 2d, 2e). No circumferential enhancement was observed around any of the tumors. 3D-CEUS further visually and stereospecially showed that the blood supply of the tumors was derived from tortuous trophoblast vessels around the affected side ovary and presented radially irregular branches (Fig. 1g, 2f). The relevant parameters of CEUS for tumors were analyzed as shown in Table 1. Compared with the myometrium, the relevant angiographic parameters: RT, TTP, PI, AUC and HT were significantly different($P < 0.05$).

Table 1
Comparison of quantitative parameters of TIC between ovarian SSPBT lesion and myometrium.

Group	Number	RT (s)	TTP (s)	PI (dB)	AUC (dB.s)	HT (s)	MCT (s)
SSPBT	6	15.48 ± 1.67	25.43 ± 1.59	14.47 ± 2.03	1470.99 ± 284.20	77.15 ± 7.80	18.62 ± 2.48
Myometrium	6	19.01 ± 2.42	32.83 ± 2.74	23.15 ± 8.78	2859.18 ± 336.4	120.50 ± 9.66	26.23 ± 4.84
P value		0.008	0.008	0.003	0.001	0.038	0.031

myometrium.

Note: SSPBT, serous surface papillary borderline tumor. TIC, contrast time-intensity curve. RT, rising time. TTP,time to peak. PI, peak intensity. AUC, area under the curve. HT, half time of descending peak intensity. MCT, mean channel time.

3.3 Clinical features

The clinical data of the 5 patients are shown in Table 2. Three patients had SSPBT on one ovary, while the contralateral ovary was normal, and 2 patients had SSPBT on both ovaries.The clinical symptoms of the patients were not specific. 3 cases were found with pelvic mass during physical examination.1 case was treated for abdominal pain for more than one month, and another case was found ovarian tumor during cesarean section.CA125 was elevated in 4 patients (80%), of which, CA199 increased in 1 patient. CEA levels in all 5 patients were in the normal range.

Table 2
The clinical data of patients with SSPBT.

Case	Age	Pregnancy history	CA125(U/ml)	Affected side	Pelvic implant nodules	Ascites	FIGO stage	Tumor recurrence
1	43	G1P1	872.60	Bilateral	Multiple nodules	Moderate	IIIA2	None
2	22	G0P0	719.00	Left	Multiple nodules	Small	IIIA2	None
3	24	G0P0	312.00	Bilateral	None	Small	IC3	None
4	38	G2P2	122.30	Right	None	Small	IC3	None
5	42	G3P1	31.56	Right	None	None	IC2	None

Note: SSPBT, serous surface papillary borderline tumor. CA125, carbohydrate antigen 125. FIGO, international federation of obstetrics and gynecology surgery.

During the operation, the tumors were all without capsule and showed a large number of white and bright beadlike nodules which were fused into a vegetable pattern(Fig. 2g), among which 3 cases (60%) had implant nodules in the pelvic cavity and 4 cases (80%) had light yellow ascites with minimal to moderate amount. One patient received radical surgery. One underwent bilateral ovarian mass removal and the other three underwent lateral adnexectomy. There was no tumor recurrence in 1–2 years follow-up, in which one 24-year-old patient with bilateral SSPBT was successfully pregnant and delivered by assisted technology.

3.4 Pathologic findings

Pathological examination of 5 cases showed surface papillary borderline tumor of the ovary. Microscopically, the tumor cells showed papillary hyperplasia and borderline shape. Many dilated blood vessels were found in the axis of fibrous connective tissue in the center of papilla (Figure. 1h) and sand bodies with different numbers could be observed (Figure. 2h).The pelvic organs involved, peritoneal nodules were noninvasive and nuclear heterogenous cells from ovary were found in ascites cell sediment wax. None of the lymph nodes examined were involved. According to the FIGO staging, there were 3 cases of stage I (60%) and 2 cases of stage III (40%).

4. Discussions

Ovarian SSPBT grows on the surface of the ovary without capsule which is prone to non-invasive peritoneal implantation[5]. We believe that the characteristic ultrasonic manifestations of SSPBT are closely related to its pathological structure. On gray-scale ultrasound, SSPBT showed irregular solid echo around the normal ovary,where a large number of dense small anechoic areas accompanied by short line strong in their posterior wall were observed. It may be the unique physical characteristics of ultrasound formed by the fusion of a large number of dense distribution of transparent ichthous nodules. In addition, different degrees of speckled strong echo could be seen in ultrasonography, and when they were abundant, "blizzard" sign could be observed. We believe that it is the unique ultrasonic feature of the large amount of sand in the shaft axis of papillary fibers pathologically. Some researchers believed that the presence of tumor sand bodies meant that they had good biological behavior and prognosis[12].The presence of sand bodies could block the growth of tumor cells and even formed a barrier for tumor metastasis[13].

Ultrasound can sensitively show implantable pelvic nodules, especially in the presence of ascites. It should be noted that when there is no or a small amount of pelvic effusion, the mass is easily disturbed by the strong echo of gas in the abdominal pelvic intestinal tube. In our study, 1 case of missed diagnosis may be caused by the increased uterine and pelvic intestinal gas during pregnancy, which also reminds us that special attention should be paid to the periovarian condition during the accessory area scanning, and the periovarian lesions can be observed by using the dual-combination method of pressure probe.

The density, morphology, distribution and function of new microvessels in tumor stroma are the pathological basis of CEUS perfusion imaging[7, 14]. Compared with the blood supply of benign ovarian

tumors and normal tissues, the progressive proliferation of ovarian borderline tumors and malignant tumors depends on the establishment of their complex blood supply network. The increased number of microvessels in them is irregular in shape, which can be manifested as tortuous and thickened or slender, increased microvascular permeability, and arterio-venous short circuit[14].As a blood pool development technology, CEUS can objectively evaluate the blood perfusion characteristics of tumors by displaying the blood perfusion of ovarian tumors in real time and quantitatively analyzing the time-enhancement information of tumor contrast[7–9]. In our study, ovarian SSPBT in conventional doppler ultrasound showed only mild to moderate blood flow signals, the information derived from tumor blood flow was scarce and limited. However, on 2D-CEUS, it presented multiple branches of the massive vessels around the ovary which were eccentric and unevenly perfused, with no obvious enhancement of the defect area could be observed, and compared with the myometrium, the enhancement was characterized by synchronous or late low enhancement of the uterine wall and rapid regression. 3D-CEUS can further demonstrates the entry path, spatial distribution and relationship with peripheral blood vessels of tumor trophoblast vessels[9]. In our study, multiple tortuous branches of SSPBT nourishing vessels emanating from around the ovary were stereosporically displayed in 3D-CEUS. Kim et al. reported the papillary structure with internal branching pattern of SSPBT from the perspective of MR images, and believed that this was a manifestation of its good differentiation [15]. Different from previous studies, we analyzed the blood perfusion characteristics of SSPBT from 2D-CEUS and 3D-CEUS and analyzed the pathological characteristics of SSPBT.We speculated that the perfusion characteristics of SSPBT might be closely related to the more dilated microvessels seen in the axis of papillary fibrous vessels on the pathological structure. In addition, we performed quantitative evaluation of SSPBT perfusion, and the results showed that the RT,TTP,PI,AUC and HT of the tumor were statistically significant compared with the myometrium(0.05).

Fertility preserving surgical treatment which is the standard treatment for young BOTs (recommended grade A) is a comprehensive staging surgery. Compared with radical surgery, postoperative recurrence rate will be increased, but there is no significant difference in overall survival rate [16]. The surgical scope of staging surgery, especially ovarian tumor exfoliation, was of great benefit to the postoperative pregnancy success rate[16, 17]. In this study, a young patient who underwent bilateral SSPBT stripping was successfully pregnant and delivered one year later by assisted technology.

The tumor marker CA125 is mainly expressed in ovarian serous tumors, but the level of CA125 can be overlaps between SSPBT and serous papillary carcinoma [18]. CA125 combined with ultrasonography can be used to monitor postoperative tumor recurrence in serous borderline tumors [19].In this study, 4 cases (80%) of SSPBT showed different levels of serum CA125 increased before operation, but no tumor recurrence was found in regular ultrasound and follow-up of serum CA125 level one year after operation. Due to the tendency of long-term recurrence of borderline tumors, long-term rigorous follow-up of more than 10 years is still needed after operation.

Above all, ovarian SSPBT on the multimodal ultrasonic which includes gray-scale ultrasound, 2D-CEUS and 3D-CEUS have unique sonographic features that are closely related to the pathological structure of the tumor. Ultrasound plays an important role in the diagnosis and postoperative follow-up of SSPBT. Because of the low incidence of the ovarian SSPBT, the cases we collected may not be fully reflected in the whole image characteristics of these tumors, but in any case, we believe that our research will make a useful contribution to the future study of SSPBT.

List Of Abbreviations

SSPBT, ovarian serous surface papillary borderline tumor;

2D-CEUS, two di-mensional contrast enhanced ultrasonography;

3D-CEUS, three di-mensional contrast-enhanced ultrasonography;

RT, Angiographic rising time;

TTP, time to peak;

PI, peak intensity;

AUC, area under the curve;

HT, half time of descending peak intensity;

BOTs, borderline ovarian tumors;

SBT, Serous borderline tumor;

CDFI, the color doppler flow imaging;

FIGO, the international Federation of Obstetrics and Gynecology Surgery;

IOTA, the International Ovarian tumor Analysis;

TIC, time-intensity curve;

RI, resistance index;

CEA, carcinoembryonic antigen;

CA199, carbohydrate antigen 19 – 9;

CA125, carbohydrate antigen 125.

Declarations

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Authors' contributions

L G and L X: contributed to the conception of the study, data acquisition and approved the final version. X L, H L, L H, F C, M C and X W: provide assistance for data acquisition analyses. L X: wrote the manuscript. L J and L X: contributed to analysis and manuscript preparation.

Consent for publication

Not applicable

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Conflicts of interest

All authors have no conflicts of interest to declare.

Ethics approval and consent to participate

This study was approved by the institutional ethics committee of The First Affiliated Hospital of Fujian Medical University, and the informed consent was signed by all participants.

Statement

We confirm that all methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

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Figures

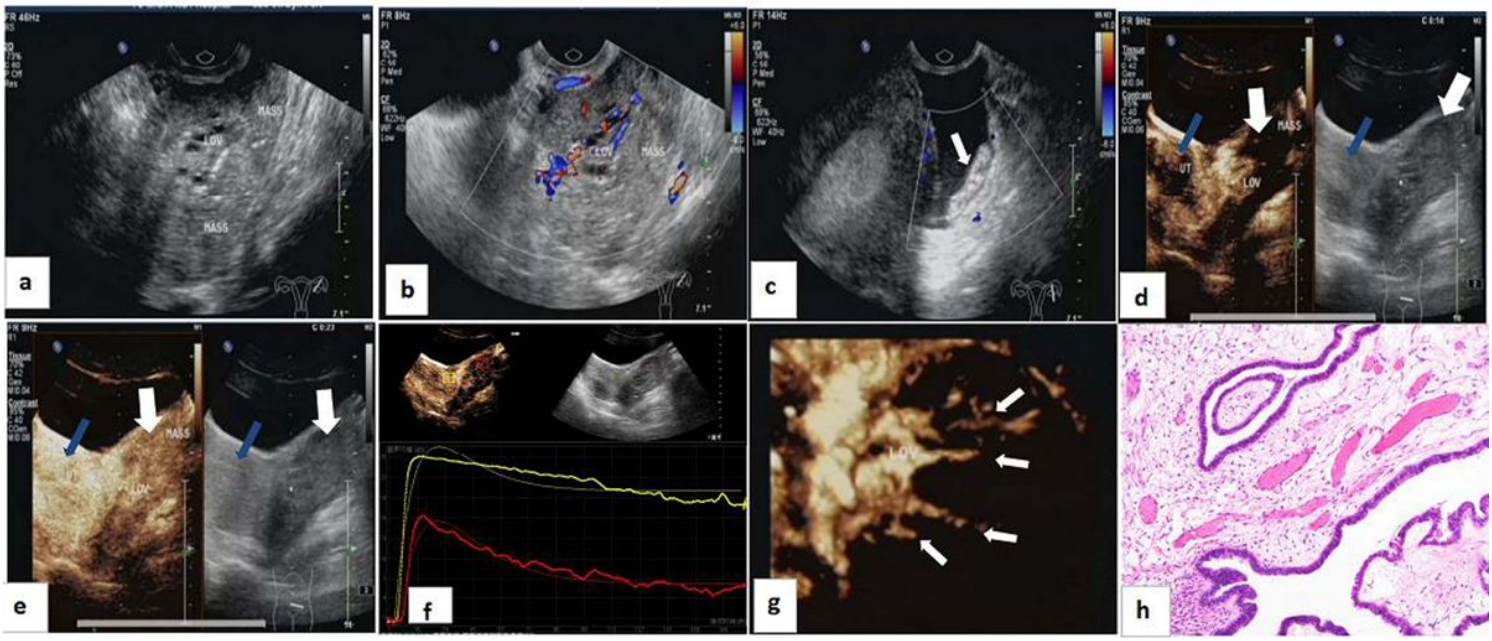

Figure 1

Multi-mode ultrasound and pathological features of left ovarian SSPBT in case 2. a. A large area of substantial echo was observed around the left ovary,inside which there were dense small echo-free areas and scattered speckled strong echo b. CDFI showed more blood flow signals in the tumor. IOTA score was 3 points c. Pelvic retroperitoneal implantation nodule (white arrow) in which point-like blood flow signals were observed. d-e. Left periovarian mass began (white arrow) to strengthen later than uterine wall (blue arrow) on 2D-CEUS (d), and reached peak intensity(e). f. The contrast TIC curves of lesions and myometrium : red for lesions and yellow for myometrium. g. Tumor trophoblastic blood vessels originated from around the left ovary and presented radial branches on 3D-CEUS (white arrow) . h. Photomicrograph of a histological specimen showing papilla/micropapilla structures covered by monolayer or lamellar cubed to columnar cells and more small blood vessels with dilatation and congestion in the axis of fibrous connective tissue (hematoxylin-eosin staining, the original magnification×200). IOTA, international analysis of ovarian tumors; SSPBT, borderline serous surface papillary borderline tumor. UT, uterine. OV, ovary

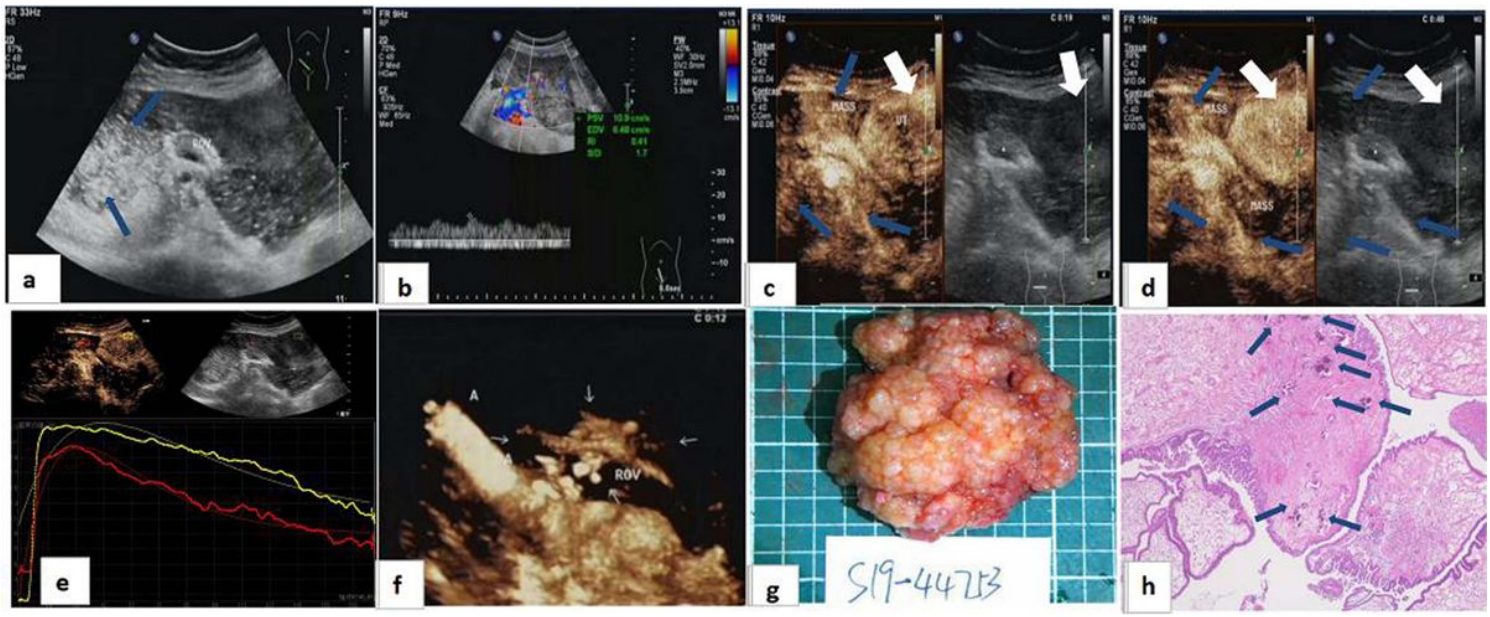

Figure 2

Multi-mode ultrasound and pathological features of left ovarian SSPBT in case 1. a. A large area of substantial echo around the right ovary was found, in which a large number of speckled strong echogenicity was seen, showing snowstorm sign (blue arrow). b. The spectrum Doppler showed that the maximum velocity of tumor systole (PSV) was about 10.9 cm per second, the blood flow resistance index (RI) was about 0.41, and IOTA score was 3 points. c-d. The right periovarian masses showed synchronous low enhancement (c,blue arrow) and subsided faster (d, blue arrow) compared to the uterine wall (d, white arrow). e. TIC curves of lesions and myometrium : red for lesions and yellow for myometrium. f. 3D-CEUS showing that the tumor supplied by a large branching blood vessel around the right ovary (white arrow). g. Macroscopic view of tumor. h. Microscopically, papilla/micropapilla structures covered by monolayer or lamellar cubic cells to columnar cells and a large amount of sand and gravel bodies(blue arrow) in the axis of fibrous connective tissue were observed (Hematoxylin-eosin staining, original magnificationX200). IOTA, international ovarian tumor analysis. SSPBT, borderline serous surface papillary borderline tumor . UT, uterine. OV, ovary