

Imaging in gynecological disease (16): clinical and ultrasound characteristics of serous cystadenofibromas in adnexa

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KEYWORDS: ovarian neoplasm; serous cystadenofibroma; ultrasonography

CONTRIBUTION

What are the novel findings of this work?

This study describes the ultrasound characteristics of histologically confirmed serous cystadenofibromas in the adnexa.

What are the clinical implications of this work?

The possibility to recognize the typical ultrasound features of various adnexal pathologies is helpful when selecting treatment for women with an adnexal mass. Many cystadenofibromas contain papillary projections, so they may be confused with malignancies, in particular with borderline tumors.

ABSTRACT

Objective To describe the clinical and ultrasound characteristics of serous cystadenofibromas in the adnexa.

Methods This was a retrospective study of patients identified in the International Ovarian Tumor Analysis (IOTA) database, who had a histological diagnosis of serous cystadenofibroma and had undergone preoperative ultrasound examination by an experienced ultrasound

examiner, between 1999 and 2012. In the IOTA database, which contains data collected prospectively, the tumors were described using the terms and definitions of the IOTA group. In addition, three authors reviewed, first independently and then together, ultrasound images of serous cystadenofibromas and described them using pattern recognition.

Results We identified 233 women with a histological diagnosis of serous cystadenofibroma. In the IOTA database, most cystadenofibromas (67.4%; 157/233) were described as containing solid components but 19.3% (45/233) were described as multilocular cysts and 13.3% (31/233) as unilocular cysts. Papillary projections were described in 52.4% (122/233) of the cystadenofibromas. In 79.5% (97/122) of the cysts with papillary projections, color Doppler signals were absent in the papillary projections. Most cystadenofibromas (83.7%; 195/233) manifested no or minimal color Doppler signals. On retrospective analysis of 201 ultrasound images of serous cystadenofibromas, using pattern recognition, 10 major types of ultrasound appearance were identified. The most common pattern was a unilocular solid cyst with one or more papillary projections, but no other solid components

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(25.9%; 52/201). The second most common pattern was a multilocular solid mass with small solid component(s), but no papillary projections (19.4%; 39/201). The third and fourth most common patterns were multi- or bilocular cyst (16.9%; 34/201) and unilocular cyst (11.9%; 24/201). Using pattern recognition, shadowing was identified in 39.8% (80/201) of the tumors, and microcystic appearance of the papillary projections was observed in 34 (38.6%) of the 88 tumors containing papillary projections.

Conclusions The ultrasound features of serous cystadenofibromas vary. The most common pattern is a unilocular solid cyst with one or more papillary projections but no other solid components, with absent color Doppler signals. Most serous cystadenofibromas were poorly vascularized on color Doppler examination and many manifested acoustic shadowing. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Aim

To describe the clinical and sonographic characteristics of serous cystadenofibromas in the adnexa.

Background

Epidemiology

Cystadenofibromas are defined by the World Health Organization (WHO) as tumors composed predominantly of benign-appearing stroma derived from the ovarian stroma¹. They contain dominant stromal proliferations that overshadow the epithelial element. When the stroma is highly cellular and fibrous and forms large solid areas containing scattered glands or thick papillary projections, the tumor is called adenofibroma; if there is a cystic component, it is called cystadenofibroma².

Cystadenofibromas occur in women of all ages, but most frequently in those aged between 40 and 60 years. The true prevalence of cystadenofibromas is uncertain³. Cystadenofibromas and adenofibromas, together with cystadenomas, comprise two-thirds of all benign ovarian epithelial neoplasms². Even though mucinous, endometrioid and clear-cell cystadenofibromas exist, they are very rare². The present study focuses on serous cystadenofibromas.

Microscopy

Serous cystadenofibromas display an epithelial lining lacking proliferation. The stroma can resemble normal ovarian stroma, but it is more fibrous or edematous². The stromal component is essentially identical to that of ovarian fibromas. Seidman and colleagues have proposed an interesting hypothesis on how serous cystadenofibromas arise. They hypothesized that serous cystadenofibromas are ovarian stromal neoplasms, i.e.

fibromas that have encompassed glandular inclusions, adhesions or both⁴. The papillary projections of the cystadenofibromas have been described as short, broad structures composed of fibrous tissue⁵.

Macroscopy

Macroscopically, serous cystadenofibromas are composed of cysts filled with clear watery fluid or thin mucoid material. Occasionally, these cysts contain thicker mucus-like material, but this is more typical of mucinous cystadenofibromas. The external surface of serous cystadenofibromas is generally smooth and glistening but, occasionally, there are papillary excrescences on the external surface of the lesion. The internal lining of the cysts is either flat or may have a varying number of coarse papillary projections. Serous cystadenofibromas vary in size²; they may have a diameter of up to 30 (mean, 5–8) cm.

Clinical symptoms and prognosis

The symptoms and signs associated with serous cystadenofibromas are unspecific. The most common symptoms are pelvic pain and discomfort, but many cystadenofibromas are diagnosed in asymptomatic women, especially if the lesions are small². While serous cystadenofibromas are benign tumors, they may look malignant macroscopically and on medical imaging^{6–9}.

METHODS

This was a retrospective study of patients, identified in the International Ovarian Tumor Analysis (IOTA) database, who had a histological diagnosis of serous cystadenofibroma and had undergone preoperative ultrasound examination, by an experienced ultrasound examiner, between 1999 and 2012 (IOTA phases 1, 1b, 2 and 3)^{10–13}. Clinical and ultrasound information in the IOTA database is collected and entered into the database prospectively. All patients had been examined with transvaginal ultrasound (supplemented with a transabdominal scan, if necessary) using a standardized examination technique, which followed a strict research protocol, and all masses were described using the standardized IOTA terminology¹⁴. Most examinations had been carried out using high-end ultrasound equipment, the frequency of the vaginal probes varying between 5.0 and 9.0 MHz and that of the abdominal probes between 3.5 and 5.0 MHz. In cases of bilateral masses, that representing the cystadenofibroma was included. If both masses were cystadenofibromas, the data from the dominant mass were used for statistical analysis. The dominant mass is the one with the most complex ultrasound appearance; if both masses manifest similar ultrasound morphology, the dominant mass is the largest one or the one most easily accessible using ultrasound. Using IOTA terminology, a papillary projection is defined as a projection of solid tissue into a cyst cavity, with a height of at least 3 mm¹⁴. Papillary projections differ from

other solid components in that they protrude into the cyst cavity, while other solid components do not (Figure S1). Results of Doppler examinations are reported in terms of a color score¹⁴. A color score of 1 means that no color or power Doppler signals are detected in the tumor; a score of 2 that minimal color Doppler signals are detected; a color score of 3 that moderate color Doppler signals are detected; and a score of 4 that abundant color Doppler signals are detected.

In addition to using the prospectively collected clinical and ultrasound data in the IOTA database, we assessed retrospectively ultrasound images of serous cystadenofibromas using pattern recognition¹⁵. Ultrasound images were available for 135 serous cystadenofibromas in the IOTA database. We also assessed ultrasound images of 66 histologically confirmed serous cystadenofibromas examined outside the IOTA phase-1, -1b, -2 and -3 studies. These 66 cases were identified from the databases of the participating ultrasound centers, and six of these cases are also included in the ongoing IOTA phase-5 study. Three authors (A.C.T., B.A.V. and L.V.) reviewed independently 201 ultrasound images of serous cystadenofibromas (most of them electronically). They used pattern recognition to identify possible typical ultrasound patterns. Finally, the three authors assessed all 201 ultrasound images together to reach consensus. Their agreed description was used for statistical calculations. Shadowing was noted as being present or absent and the appearance of any solid component was classified as microcystic or not microcystic. Microcystic appearance of papillary projections is illustrated in Figure S2.

All clinical and ultrasound information was entered into a dedicated Excel file which was used for statistical analysis (Microsoft Office Excel 2003, Redmond, WA, USA).

RESULTS

Clinical background data for the 233 patients in the IOTA database with histologically confirmed serous cystadenofibroma are shown in Table 1. Median age was 54 (range, 14–89) years and 63% of the patients were postmenopausal.

Table 1 Clinical characteristics of 233 women with serous cystadenofibroma included in International Ovarian Tumor Analysis (IOTA) study

Characteristic	Value
History of ovarian cancer	
Family	4 (1.7)
Personal	0 (0)
Age (years)	54 (14–89)
Postmenopausal	147 (63.1)
Nulliparous*	38 (28.6)
Tender mass when pressed with vaginal probe†	4 (4.0)
CA 125 (U/mL)‡	46 (2–1808)

Data are given as *n* (%) or median (range). Data available in: *133 cases (parity not recorded in IOTA phase-3 study); †100 cases (tenderness recorded only in IOTA phase-3 study); ‡162 cases. CA 125, cancer antigen 125.

The sonographic characteristics of cystadenofibromas, as reported in the IOTA database, and the diagnosis suggested by the original ultrasound examiner are presented in Table 2. Median largest tumor diameter

Table 2 Sonographic characteristics of 233 serous cystadenofibromas included in International Ovarian Tumor Analysis (IOTA) study and diagnosis suggested by original ultrasound examiner

Characteristic	Value
Bilateral masses	37 (15.9)
Largest diameter of lesion (mm)	76 (21–350)
Type of mass	
Unilocular	31 (13.3)
Multilocular	45 (19.3)
Unilocular-solid	67 (28.8)
Multilocular-solid	85 (36.5)
Solid	5 (2.1)
Echogenicity of cyst fluid	
Anechoic	148 (63.5)
Low-level	61 (26.2)
Ground glass	5 (2.1)
Mixed	14 (6.0)
No cyst fluid	5 (2.1)
Largest diameter of largest solid component (mm)*	17 (3–93)
Papillary projection(s)	122 (52.4)
Number of papillary projections	
1	64 (52.5)
2	21 (17.2)
3	16 (13.1)
> 3	21 (17.2)
Height of largest papillary projection (mm)	5 (3–44)
Flow in papillary projection	25 (20.5)
Shadowing	23 (9.9)
Ovarian crescent sign†	25 (39.1)
Ascites	2 (0.9)
Fluid in pouch of Douglas	35 (15.0)
Fluid in pouch of Douglas (mm)‡	16 (1–31)
Color score	
1	96 (41.2)
2	99 (42.5)
3	37 (15.9)
4	1 (0.4)
Diagnosis based on subjective assessment	
Benign	183 (78.5)
Borderline or malignant	50 (21.5)
Specific diagnosis§	
Dermoid	6 (2.8)
Simple cyst/paraovarian cyst	13 (6.2)
Functional ovarian cyst	6 (2.8)
Hydrosalpinx	5 (2.4)
Peritoneal pseudocyst	2 (0.9)
Abscess	1 (0.5)
Fibroma/fibrothecoma	4 (1.9)
Serous cystadenoma/cystadenofibroma	87 (41.2)
Mucinous cystadenoma/cystadenofibroma	18 (8.5)
Cystadenofibroma	1 (0.5)
Cystadenoma	7 (3.3)
Primary invasive tumor	7 (3.3)
Borderline tumor	34 (16.1)
Other malignant tumor	3 (1.4)
Not possible	17 (8.1)











Data are given as *n* (%) or median (range). *Solid component present in 157 masses. †Data available in 64 cases (obligatory information only in IOTA phase-3 study). ‡Data available in all 35 cases with fluid in pouch of Douglas. §Data available in 211 cases (not obligatory to suggest specific diagnosis in IOTA phase-1b study).

was 76 (range, 21–350) mm. Most tumors (157/233; 67.4%) were described as containing solid components, but 19.3% (45/233) were described as multilocular cysts and 13.3% (31/233) as unilocular cysts. Papillary projections were described in 52.4% (122/233) of the cystadenofibromas and in 52.5% (64/122) of these only one papillary projection was present. In 79.5% (97/122) of the cysts with papillary projections, color Doppler signals were absent in the papillary projections. Shadowing was described in 9.9% (23/233) of serous cystadenofibromas. Most cystadenofibromas (83.7%; 195/233) manifested no or minimal color Doppler signals. The original ultrasound examiner suspected malignancy in 21.5% (50/233) of the cystadenofibromas, and in most of these cases (34/50), a borderline tumor was suspected. Of the 50 cystadenofibromas suspected to be malignant, 39 (78.0%) were described on ultrasound as having papillary projections, compared with 83/183 (45.4%) of those judged to be benign.

When analyzing ultrasound images of 201 serous cystadenofibromas using pattern recognition, 10 major patterns were identified. These are shown together with

their prevalence in Table 3. The most common pattern was a unilocular solid cyst with one or more papillary projections but no other solid components (25.9%; 52/201). The second most common pattern was a multilocular solid mass with small solid component(s) but no papillary projections (19.4%; 39/201). The third and fourth most common patterns were multi- or bilocular cyst (16.9%; 34/201) and unilocular cyst (11.9%; 24/201). The patterns can be collapsed into five larger groups: unilocular or multilocular cysts with no solid components (58/201; 29%); cysts with papillary projections but no other solid components (72/201; 35.8%); cysts with solid components other than papillary projections, but no papillary projections (53/201; 26.4%); cysts with both papillary projections and other solid components (16/201, 8.0%); and purely solid tumors (2/201; 1.0%). Shadowing was identified in 39.8% (80/201) of the tumors. Microcystic appearance of papillary projections was observed in 34 (38.6%) of the 88 tumors containing papillary projections. Ultrasound images illustrating the ultrasound patterns are shown in Figures 1–7.

Table 3 Ultrasound patterns of 201 serous cystadenofibromas identified using pattern recognition

Pattern	Characteristics	Tumors	No shadowing*	Shadowing*	Microcystic appearance of papillary projections*
	Unilocular cyst	24 (11.9)	24 (11.9)	0 (0)	N/A
	Bilocular cyst	9 (4.5)	9 (4.5)	0 (0)	N/A
	Multilocular cyst	25 (12.4)	25 (12.4)	0 (0)	N/A
	Unilocular solid cyst with papillary projection(s) but no other solid components	52 (25.9)	30 (14.9)	22 (10.9)	22 (10.9)
	Multilocular solid cyst with papillary projection(s) but no other solid components	20 (10.0)	9 (4.5)	11 (5.5)	7 (3.5)
	Multilocular solid cyst with small solid component(s) but no papillary projections	39 (19.4)	14 (7.0)	25 (12.4)	N/A
	Multilocular solid cyst with large solid component(s) but no papillary projections	14 (7.0)	5 (2.5)	9 (4.5)	N/A
	Multilocular solid cyst with both papillary projection(s) and small or large other solid component(s)	15 (7.5)	4 (2.0)	11 (5.5)	4 (2.0)
	Unilocular solid cyst with both papillary projection(s) and other solid component(s)	1 (0.5)	0 (0)	1 (0.5)	1 (0.5)
	Solid mass	2 (1.0)	1 (0.5)	1 (0.5)	0 (0)
Total		201	121	80	34

Data are given as *n* (%). In multilocular solid tumors, solid components were judged to be large if, subjectively, they constituted large proportion of lesion. *Percentages calculated per all 201 cystadenofibromas. N/A, not applicable.

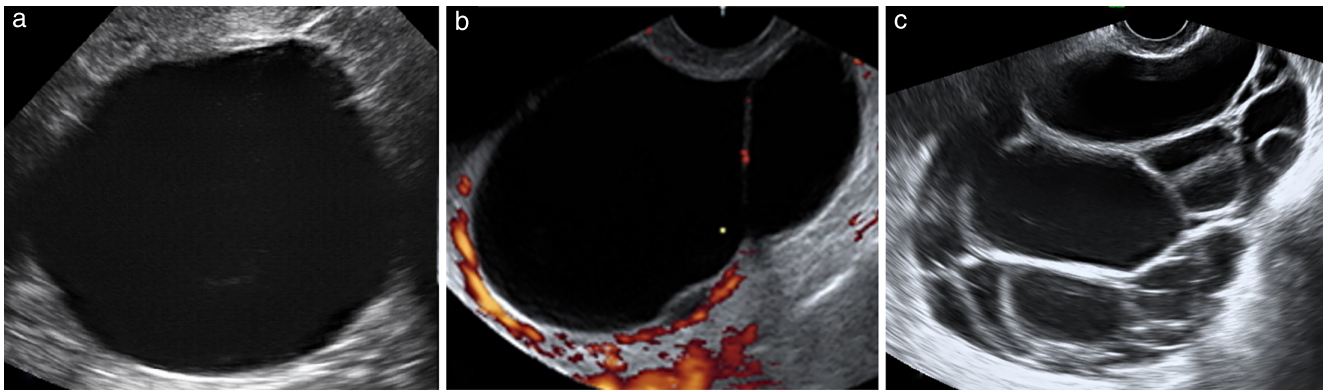


Figure 1 Ultrasound images of serous cystadenofibromas with no solid components. (a) Unilocular serous cystadenofibroma in 53-year-old woman. (b) Bilocular serous cystadenofibroma in 45-year-old woman. (c) Multilocular serous cystadenofibroma in 49-year-old woman.

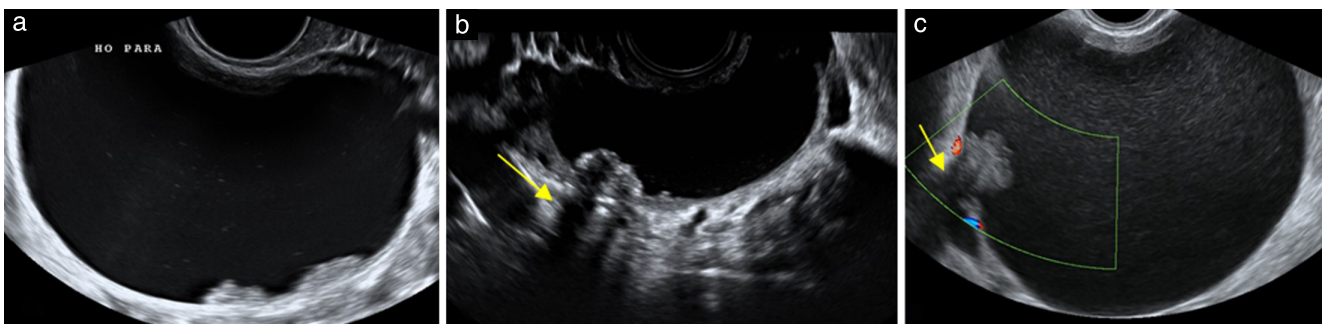


Figure 2 Ultrasound images of unilocular solid serous cystadenofibromas with papillary projections but no other solid components: (a) in 19-year-old woman, showing no shadowing; (b) in 15-year-old woman, showing shadowing (arrow); and (c) in 61-year-old woman, showing papillary projections with microcystic appearance and shadowing (arrow).

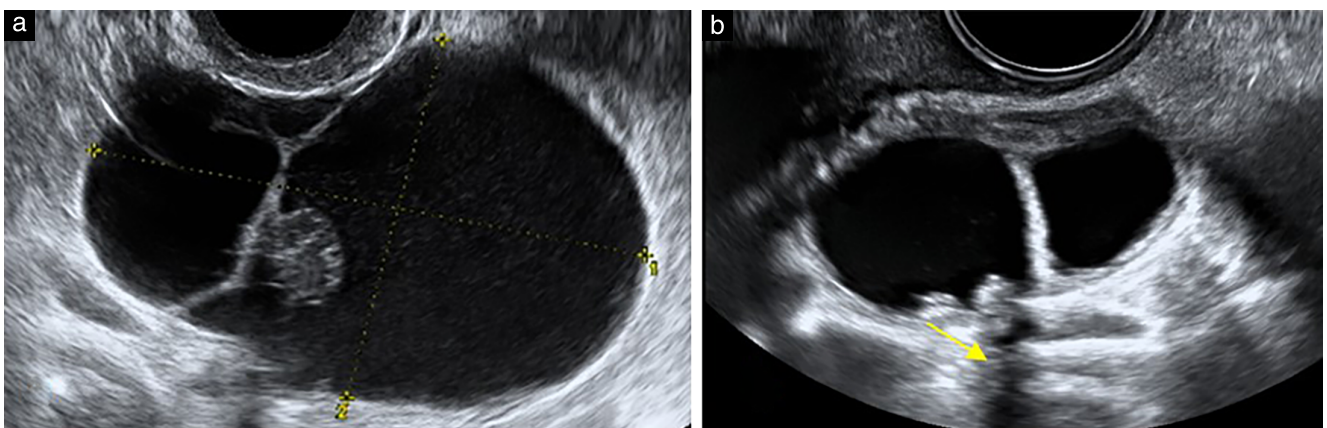


Figure 3 Grayscale ultrasound images of multilocular solid serous cystadenofibromas with papillary projections but no other solid components: (a) in 48-year-old woman, showing papillary projection with microcystic appearance; and (b) in 34-year-old woman, showing shadowing (arrow) behind a papillary projection.

DISCUSSION

In this retrospective study, we identified, using pattern recognition, 10 ultrasound patterns of serous cystadenofibromas in the adnexa. We found the most common pattern to be a unilocular solid cyst with papillary projections but no other solid components, and the second most common to be a multilocular solid mass with

small solid component(s) but no papillary projections. On retrospective assessment of ultrasound images, shadowing was found to be present in 39.8% (80/201) of the serous cystadenofibromas. Other typical features were microcystic appearance of the papillary projections (seen in almost 40% of all cystadenofibromas with papillary projections) and absence of color Doppler signals in the papillary

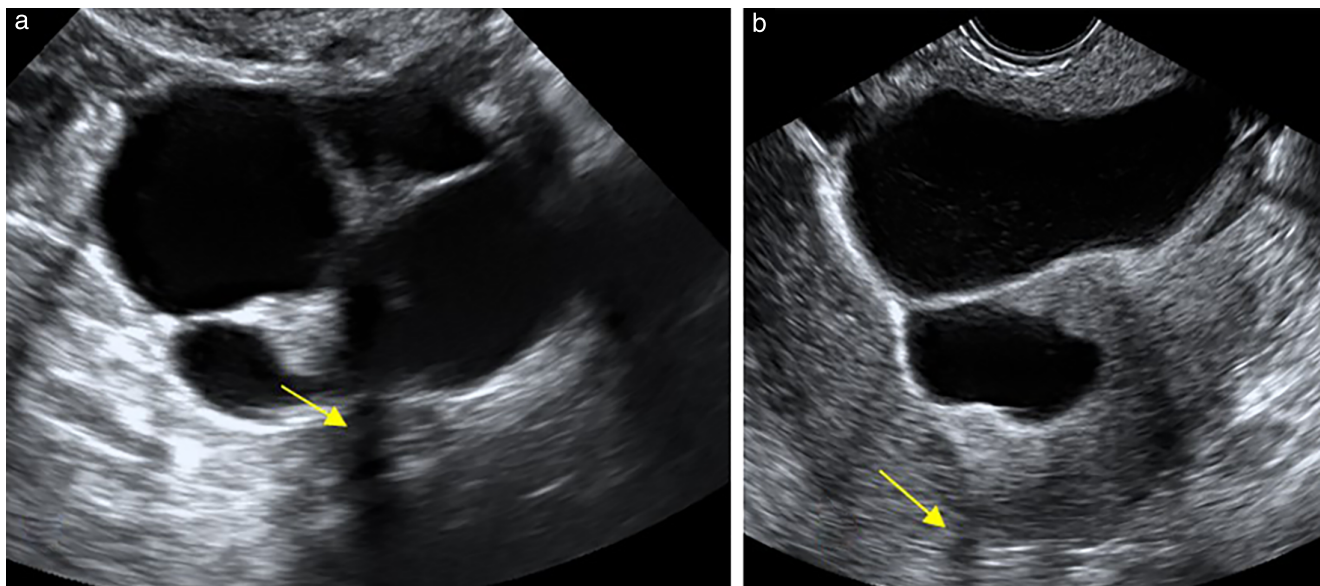


Figure 4 Grayscale ultrasound images of multilocular solid serous cystadenofibromas with solid components but no papillary projections: (a) in 52-year-old woman, showing small solid components with shadowing (arrow); and (b) in 77-year-old woman, showing large solid component with shadowing (arrow).



Figure 5 Grayscale ultrasound image of a multilocular solid serous cystadenofibroma with large solid component and papillary projections in 64-year-old woman. Shadowing (arrow) is seen.

projections (absent in 80% of the cystadenofibromas with papillary projections). The serous cystadenofibromas varied greatly in size and most of them were poorly vascularized on color Doppler examination.

To the best of our knowledge this is the largest series describing the ultrasound characteristics of histologically confirmed serous cystadenofibromas in the adnexa. A limitation of this study is that it is retrospective. Ultrasound images were not available for all cases, and this may have limited the possibility to detect typical ultrasound features. Moreover, we have information from only the largest or the most complex mass in cases of bilateral masses, and this may have introduced bias. It may seem

surprising that shadowing was recorded prospectively in the IOTA database in only about 10% of the cystadenofibromas, but in almost 40% when images were assessed to reach consensus on the ultrasound pattern. This is likely to be explained by the original ultrasound examiners not paying much attention to shadowing in the earlier phases of the IOTA studies, while, when reviewing the ultrasound images using pattern recognition in this study, shadowing was specifically sought.

Our results are in agreement with the description of serous cystadenofibromas in textbooks of pathology with regard to patient age (variable), size (variable) and macroscopic appearance (cysts filled with clear fluid with smooth internal cyst walls or with a varying number of papillary projections)^{2,16}.

Results similar to ours with regard to the ultrasound appearance of cystadenofibromas were reported in two small retrospective studies. Alcazar *et al.*¹⁷ found papillary projections or solid nodules to be present in 56% of 23 serous cystadenofibromas. Goldstein *et al.*¹⁸ reported papillary projections in 69% of 32 cystadenofibromas (30 serous and two mucinous). They emphasized that the absence of vascularization in papillary projections was a typical finding of cystadenofibromas. None of the cystadenofibromas in their series contained vascularized papillary projections or vascularized solid components. In our series, vascularized papillary projections were found in 20% of serous cystadenofibromas that contained papillary projections (Figure S3).

The differences in the ultrasound appearance of papillary projections in serous cystadenofibromas may be explained histologically. Shadowing behind a papillary projection might be due to dense fibrous tissue, while microcystic appearance might be explained by edematous areas in the papillary projection (Figures S4 and S5).

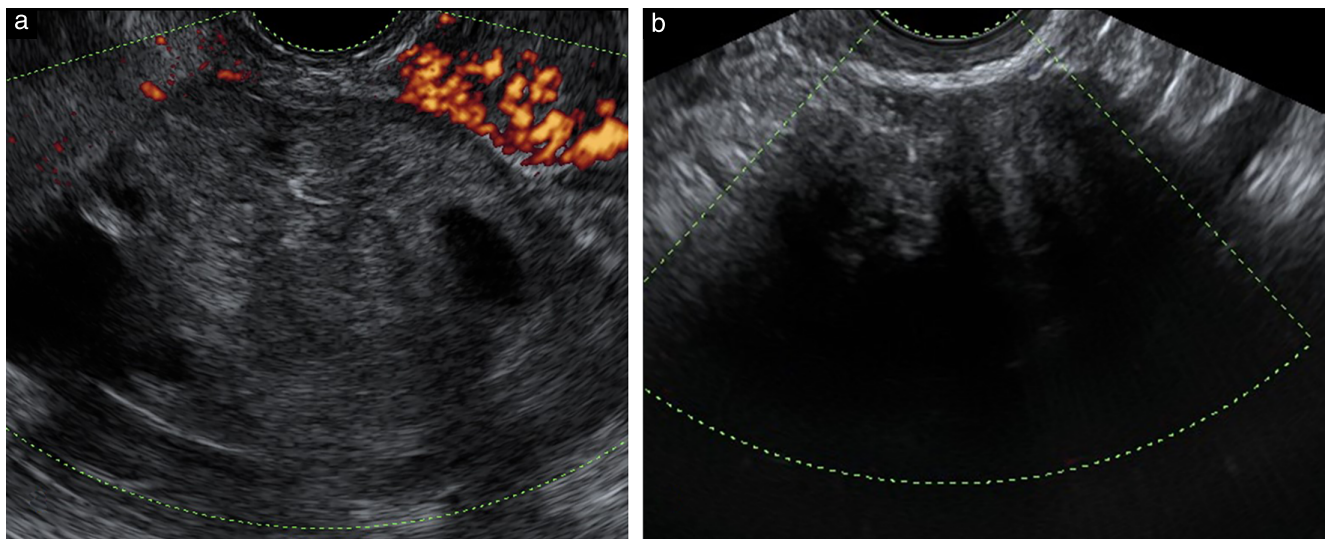


Figure 6 Power (a) and color (b) Doppler ultrasound images of solid serous cystadenofibromas in 48-year-old women. Shadowing is seen.

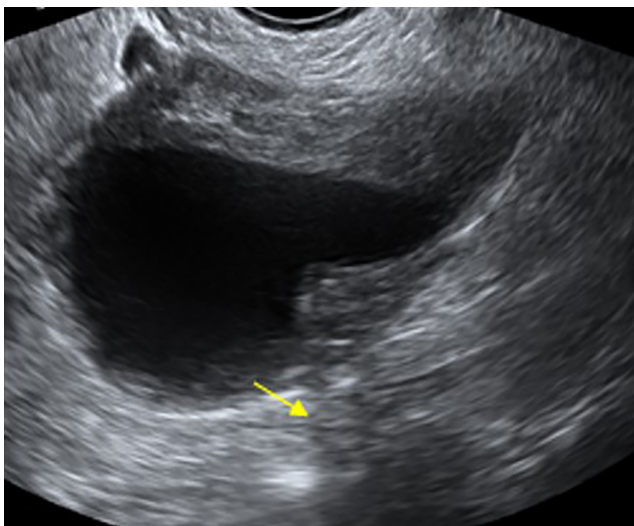


Figure 7 Grayscale ultrasound image of unilocular solid serous cystadenofibroma with solid component and papillary projection in 38-year-old woman. Shadowing (arrow) is seen.

Shadowing behind papillary projections in cystadenofibromas (Timor sign) was first reported in an oral presentation by Dr I. Timor-Tritsch at the 19th World Congress of the International Society of Ultrasound in Obstetrics and Gynecology in 2009¹⁹.

An interesting feature that might be encountered in cystadenofibromas is papillary projections on the surface of the tumor, as reported in textbooks of pathology². However, we have no information on how often this feature was seen at surgery or in the pathological specimens of our cystadenofibromas and we do not know if it would be possible to detect surface papillary projections on ultrasound. Extensive papillary projections surrounding normal ovaries has been described in serous borderline tumors²⁰.

Recognizing the typical ultrasound features of various adnexal pathologies is helpful when selecting treatment for women with an adnexal mass. In this work, we have described ultrasound features of serous

cystadenofibromas. Because many cystadenofibromas contain papillary projections, they may be confused with malignancies, in particular with borderline tumors^{21–23}. In our study, 50 serous cystadenofibromas, i.e. approximately one in five, were suspected to be malignant (most often borderline tumors) by the original ultrasound examiner, and most (78%) of those suspected to be malignant contained papillary projections. A published retrospective analysis of 204 unilocular solid cysts with papillary projections, but no other solid components, showed that shadowing behind papillary projections was more often present in benign than in borderline or malignant cysts, while papillary projections with anechoic spaces were more often present in borderline or malignant cysts than in benign cysts, i.e. in 60% vs in 24%²⁴. The finding that anechoic spaces in papillary projections was associated with malignancy is surprising in view of microcystic appearance of papillary projections being so common (38.6%) in the serous cystadenofibromas in our study. However, not all benign lesions in the study by Landolfo *et al.*²⁴ were serous cystadenofibromas, which constituted only 29% of the benign lesions. Moreover, the study of Landolfo *et al.*²⁴ included only cysts with one cyst locule and no solid components other than papillary projections.

Absence of color Doppler signals inside papillary projections and the presence of shadowing seem to be common ultrasound features of benign serous cystadenofibromas with papillary projections, but the ability of these features to discriminate between serous cystadenofibromas and borderline tumors with papillary projections needs to be investigated in a prospective study.

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We thank Dr I. Timor-Tritsch for having proposed the term microcystic to describe papillary projections containing minute cystic areas²⁵.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Figure S1 Grayscale ultrasound images of adnexal masses, illustrating International Ovarian Tumor Analysis (IOTA) criteria of papillary projection (solid tissue that protrudes into the cyst lumen with a height of at least 3 mm but with no upper limit of size) (a) and other types of solid components (solid tissue that does not protrude into cyst cavity) (b). (a) Serous cystadenofibroma in a 61-year-old patient, appearing as a unilocular-solid cyst with a papillary projection but no other solid components. (b) Stage-IA endometrioid carcinoma in an 86-year-old patient, appearing as a unilocular-solid cyst with a solid component that is not a papillary projection (reproduced from Landolfo *et al.*²⁴).

Figure S2 Grayscale ultrasound image of a unilocular solid serous cystadenofibroma in 57-year-old woman, with papillary projections that manifest microcystic appearance.

Figure S3 Power Doppler ultrasound images of serous cystadenofibromas with vascularized papillary projections in women aged (a) 15, (b) 65 and (c) 68 years.

Figure S4 Grayscale (a) and color Doppler (b) ultrasound images and hematoxylin- and eosin-stained sections (c,d) of ovarian serous cystadenofibroma. (a,b) Internal cyst wall shows a papillary projection measuring 7 × 6 × 6 mm (a), with no vascularization (b), smooth surface and shadowing (arrow). (c) Histological image shows a papillary projection (blue dotted box) with rounded shape. (d) Magnified histological image of the papillary projection shows fibromatous stroma constituting > 95% of the papillary projection covered by serous monostratified epithelium without cytological atypia; small edematous areas (constituting < 5% of the papillary projection) are visible (dashed arrow).

Figure S5 Grayscale (a) and color Doppler (b) ultrasound images and hematoxylin- and eosin-stained sections (c,d) of ovarian serous cystadenofibroma. (a,b) Internal cyst wall shows a papillary projection measuring 9 × 11 × 10 mm (a), with vascularization (b), irregular surface, no shadowing and small cystic areas inside. (c) Histological image shows a papillary projection (outlined in blue) with large edematous areas within the stroma. (d) Magnified histological image of the edematous stroma of the papillary projection surrounded by a monostratified serous epithelium.