

Clinical manifestation and pathological changes of serous papillary adenofibroma: A case series

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Received March 20, 2025; Accepted August 13, 2025

DOI: 10.3892/mco.2025.2893

Abstract. Serous papillary adenofibroma (SPAF) is a rare benign tumor in gynecological practice. Most patients have no symptoms and occasionally present with pelvic masses during physical examinations. SPAF consists of both fibrous and epithelial parts, which makes it easy to misdiagnose malignancies on pre-surgery examinations. Therefore, clinical and pathological features of SPAF at the Second Affiliated Hospital Zhejiang University School of Medicine (Hangzhou, China) were summarized in the present study to assist clinical practice. A total of 13 cases encountered at our hospital were collected and immunohistochemistry (IHC) staining was performed on their specimens. SPAF appears as a unilocular cystic mass on imaging. Serum estradiol and prolactin levels were elevated in certain patients. The IHC staining of SPAF was estrogen receptor-, progesterone receptor- and human epidermal growth factor receptor 2-positive but Ki-67- and p53-negative. The present study proved the sex hormone sensitivity of SPAF and the benign prognosis of patients. Magnetic resonance imaging is a promising method for differential diagnosis before surgery.

Introduction

Serous papillary adenofibroma (SPAF) is a rare benign gynecological tumor that is typically incidentally found during

the treatment of other diseases. As a variant of adenofibroma (AF) and cystadenofibroma (CAF), it is characterized by both fibrous and epithelial components under the microscope (1). These characteristics also become a barrier to imaging-based differential diagnosis (2). Surgeons and gynecologists sometimes misdiagnose it as a serous adenoma or even an ovarian malignancy, resulting in excessive surgery (3). Magnetic resonance imaging (MRI) is a promising tool for differentiating SPAF from cancers (2). Certain experts have summarized that the solid part of AF and CAF shows a distinguishably lower T2 and diffusion-weighted imaging (DWI) signal intensity and gains a higher apparent diffusion coefficient value than malignant neoplasms (2,4). SPAF is mainly located in the ovary, but it can be found in the fallopian tube and vulva as well (5-7). Most patients are asymptomatic unless the mass compresses the surrounding organs (7). Due to the rarity of SPAF, no specific guidelines are available and clinicians usually resect unilateral or even bilateral adnexa in practice. Early diagnosis and prevention are crucial for the treatment of SPAF (3,7,8). While most SPAF cases are benign, delayed diagnosis may lead to malignant misidentification, causing unnecessary harm and fertility impairment. The present study aimed to summarize the clinical and pathological characteristics of 13 patients with SPAF encountered at the Second Affiliated Hospital Zhejiang University School of Medicine (Hangzhou, China) and provide information to contribute to the further elucidation of SPAF. It was found that the clinical characteristics of SPAF were atypical. Conventional imaging methods such as ultrasound and CT scan offered limited evidence and a varied performance. It was also found that the MRI appearance of SPAF was uniform. In certain cases, MRI can show protrusions or papillae on the cyst wall. Immunohistochemistry (IHC) results of available slices showed that SPAF was hormone-sensitive with high expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (Her-2).

Patients and methods

Data collection. The present study was a retrospective single-center observational study. A total of 13 female patients with SPAF who underwent surgery at the Second

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Abbreviations: AF, adenofibroma; BMI, body mass index; CAF, cystadenofibroma; CT, computed tomography; E2, estrogen; FSH, follicle stimulating hormone; IHC, immunohistochemistry; MRI, magnetic resonance imaging; PRL, prolactin; PRLR, prolactin receptor; SPAF, serous papillary adenofibroma

Key words: women's health, adenofibroma, case report, immunohistochemistry, clinical characteristics

Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) from January 2018 to July 2023 were enrolled, with ages ranging from 25 to 66 years and a median age of 47 years. Preoperative laboratory results, radiological and sonographic imaging and slices of the surgical specimens were available after obtaining ethical approval. Laboratory tests were conducted according to manufacturers' instructions at the time of sample acquisition. Imaging features and diagnostic reports were generated by professional doctors according to the Ovarian-Adnexal Reporting and Data System criteria (9,10).

The inclusion criteria for this study were as follows: i) Pathologically diagnosed as SPAF; and ii) data from inpatient system since 2015. The exclusion criteria for this study were: i) Patients with other gynecological tumors or malignancies; ii) patients without abundant data, e.g., outpatients; and iii) patients with severe complications.

IHC staining and analysis. Following ethical approval, the tissue slices were uniformly collected and subjected to IHC staining and analysis on November 30th, 2023. IHC staining was performed by Zhongshan Golden Bridge Biotechnology Co. Ltd. The following steps were all performed at a laboratory room temperature of 26°C. Briefly, the acquired paraffin-embedded slices were dewaxed with xylene three times for 10 min each and dehydrated with a graded series of ethanols four times for 2 min each. Subsequently, the slices were placed in a pressure cooker (103°C) containing EDTA buffer for 2.5 min after washing five times with PBS for 2 min each. The slices were then incubated with 3% hydrogen peroxide for 10 min and washed five times with distilled water and PBS for 2 min each. Primary antibodies were then incubated at 37°C for 1 h, and secondary antibody (cat. no. PV-8000D; no dilution; Zhongshan Goldenbridge Biotechnology Co., Ltd.) was added after washing five times with PBS for 2 min each. It should be noted that the secondary antibody for Her-2 was different (cat. no. PV-8000; no dilution; Zhongshan Goldenbridge Biotechnology Co., Ltd.). Diaminobenzidine (cat. no. ZLI-9018; Zhongshan Goldenbridge Biotechnology Co., Ltd.) was added and incubated for 8 min. After washing with running water, hematoxylin and acid-fast differentiation solution (Zhongshan Goldenbridge Biotechnology Co., Ltd.) was used for counterstaining. The final pathology results were obtained by professional pathologists according to the current diagnostic criteria for p53 (cat. no. ZM-0408; no dilution; Zhongshan Goldenbridge Biotechnology Co., Ltd.), Ki-67 (cat. no. ZM-0166; no dilution; Zhongshan Goldenbridge Biotechnology Co., Ltd.), BRAF (cat. no. ZA-0668; no dilution; Zhongshan Goldenbridge Biotechnology Co., Ltd.), Wilms' tumor gene 1 (WT-1; cat. no. ZA-0559; no dilution; Zhongshan Goldenbridge Biotechnology Co., Ltd.), ER (cat. no. ZA-0102; no dilution; Zhongshan Goldenbridge Biotechnology Co., Ltd.), PR (cat. no. ZA-0255; no dilution; Zhongshan Goldenbridge Biotechnology Co., Ltd.) and Her-2 (cat. no. ZM-0065; 1:150 dilution; Zhongshan Goldenbridge Biotechnology Co., Ltd.).

Statistical analysis. All data were recorded and processed with Office 2019 (Microsoft Corporation). Count data were presented as n (%). Hypothesis testing is not applicable in this study.

Results

Clinical characteristics. The mean patient age was 43 years (range, 25-66 years). A total of four patients were menopausal. The mean body mass index of the included patients was 22.97 kg/m² (range, 15.79-28.19 kg/m²). According to the World Health Organization criteria for Asian populations (11), 7 patients were overweight, while 2 were underweight. Nearly all SPAF were located in the ovary, except for one case, where it was located in the fallopian tube (Table I).

Ovarian tumors are asymptomatic, particularly at early stages (12,13). In the present study, 10 patients were asymptomatic, of whom 40% were incidentally discovered during surgeries for other gynecological diseases, such as uterine myoma, adenomyosis and cervical cancer. Among those with symptoms, two patients had menstrual problems and two patients had mild dysmenorrhea.

Images of a typical gross appearance were found during surgery (Fig. 1A). Grossly, SPAF is a mixed neoplasm comprising cysts and solid components, but not all cases visually exhibit this characteristic. The resected specimen can help to visualize the solid components more clearly. The demarcation between the cyst (Fig. 1B, 'C') and solid component (Fig. 1B, 'S') was undefined.

Laboratory test characteristics. Carbohydrate antigens and sex hormones are two common laboratory tests for patients with ovarian masses detected before surgery. In the present study, 12 patients underwent blood tests for carbohydrate antigens (Table I). Among these patients, 8 had elevated carbohydrate antigen levels. The most common elevated carbohydrate antigen was CA125 (50%), followed by SCC (25%), CA199 (12.5%), CA153 (12.5%) and CA211 (12.5%). Of note, one patient had a significantly elevated CA125 level (818 U/ml, upper limit: 35 U/ml). We considered this as supportive evidence that demonstrated a likelihood of misdiagnosis as malignancy. After surgery, the CA125 level of this patient descended to 73.3 U/ml.

The potential effect of SPAF on sex hormone levels was then explored. A total of 10 patients had been tested for sex hormone levels. Among the patients, 4 were menopausal or peri-menopausal. The average estrogen (E2) level in menopausal patients was 199.1 pmol/l (normal range: <118.2 pmol/l for menopausal women). The other 6 patients were premenopausal with regular menstrual periods. The highest E2 level of the pre-menopausal patients was 1101.37 pmol/l and the average E2 level was 381.21 pmol/l (normal range: 71.6-529.2 pmol/l in follicular phase, 204.8-786.1 pmol/l in luteal phase). Follicle-stimulating hormone (FSH, normal range: 2.5-10.2 IU/l in follicular phase, 3.4-33.4 IU/l in ovulation period, 1.5-9.1 IU/l in luteal phase, 23.0-116.3 IU/l in menopausal women) levels of menopausal patients ranged from 32.06 to 45.53 IU/l, while the FSH level of peri-menopausal patients ranged from 3.49 to 18.59 IU/l, which was consistent with the menstrual state. The mean prolactin level (PRL; normal range: 59.00-619.00 mIU/l for non-pregnant women, 38.00-430.00 mIU/l for menopausal women) in the 10 patients was 604.34 mIU/l. Notably, 3 patients had elevated PRL levels. One of the three patients underwent pituitary MRI revealing a Rathke's cyst, with PRL concentration

Table I. Details and laboratory data of the cases (n=13).

Case no.	Age, years	Location	Manifestation	CA125, U/ml	E ₂ , pmol/l	PRL, mIU/l	Menopausal state	BMI, kg/m ²
1	49	Ovary	Null	24.7	-	-	No	24.22
2	25	Ovary	Dysmenorrhea	11.2	170.36	218.46	No	22.88
3	33	Ovary	Null	16.5	1,101.37	2,604.14	No	16.66
4	26	Ovary	Irregular menstruation and dysmenorrhea	43.5	244.46	206.13	No	15.79
5	32	Ovary	Intermenstrual bleeding	21.6	249.71	248.72	No	25.78
6	52	Ovary	Null	13.8	145.31	534.38	No	20.89
7	47	Ovary	Null	17	376.04	-	No	22.07
8	53	Ovary	Null	57.2	524.76	2,326.64	Yes	25.00
9	36	Ovary	Null	46.2	-	75.64	No	28.19
10	66	Ovary	Null	20.6	78.06	-	Yes	26.37
11	28	Fallopian tube	Null	-	-	75.43	No	22.67
12	60	Ovary	Null	17.7	138.17	-	Yes	23.44
13	52	Ovary	Null	818	55.43	150.25	Yes	24.70

E₂, estradiol; PRL, prolactin; BMI, body mass index.

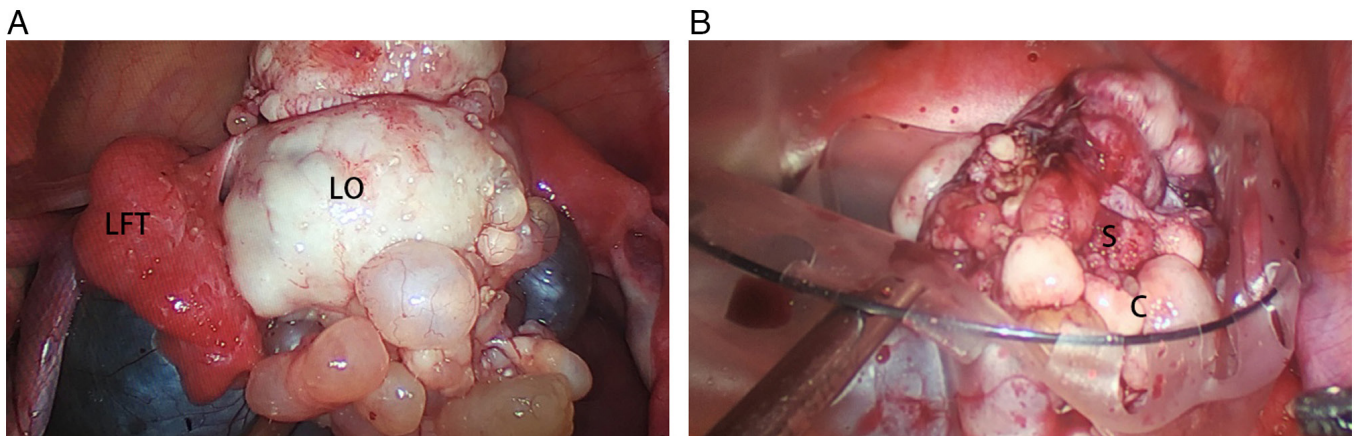


Figure 1. Gross appearance of SPAF during surgery. The images (A and B) are from a 26-year-old female patient. (A) Gross appearance before resection; a string of cysts can be seen on the surface of the ovary. (B) Gross appearance after resection; typical SPAF had multiple cysts with a solid part. LFT, left fallopian tube; LO, left ovary; S, solid part; C, cysts; SPAF, serous papillary adenofibroma.

reaching 2,604.14 mIU/l, approximately four times the upper reference limit.

Radiological and sonographic characteristics. Ultrasound is the most widely used technology in gynecology clinics. All patients completed the ultrasound test before surgery. Only 1 patient had a negative result due to a small fallopian tube SPAF. Among those with positive ultrasound findings, two had developed multicystic tumors. The echoes of the cysts varied from spotted to high-echoes. The papillae of the SPAF were small and difficult to detect. Only two sonographies revealed SPAF papillae (Fig. 2). Clinically, the appearance of SPAF is not classical. Therefore, most sonographers (76.92%) did not draw a conclusion regarding the suspected disease, while the other three mentioned differential diseases were teratomas, cystadenomas and myomas (data not shown).

The MRI appearances were more uniform than ultrasound (Table II). A total of 6 patients underwent MRI. Due to the small tumor volume, 1 MRI didn't reveal any SPAF appearance and SPAF was detected during surgery. Apart from this, 4 patients showed adnexa cyst and 1 patient displayed a pelvic mass on MRI. Low signal intensity on T1-weighted imaging (T1WI) and high signal intensity on T2WI were observed in these patients. All MRI results indicated restricted diffusion in the DWI phase. In addition, one of them observed small protrusions, which may be the papillae of the SPAF (Fig. 3). However, the radiologist initially considered the mass to be a serous cystadenoma.

Ultrasound and MRI are both widely used in gynecological imaging. However, based on the retrospective analysis of a small SPAF sample performed in the present study, it was found that MRI is more accurate and consistent than ultrasound in

Table II. Comparison of imaging features observed on ultrasound and MRI.

Imaging feature	Ultrasound detection (performed in 13 cases)	MRI detection (performed in 6 cases)
Well-defined borders	9 (69)	5 (83)
Cystic components	8 (62)	5 (83)
Papillae	2 (15)	1 (17)
T2 hyperintensity	N/A	5 (83)
T1 hypointensity	N/A	5 (83)
DWI hyperintensity	N/A	5 (83)

Values are expressed as n (%). In one case, a subcentimeter serous papillary adenofibroma focus prohibited detection of imaging features by both ultrasound and MRI. MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; N/A, not applicable.

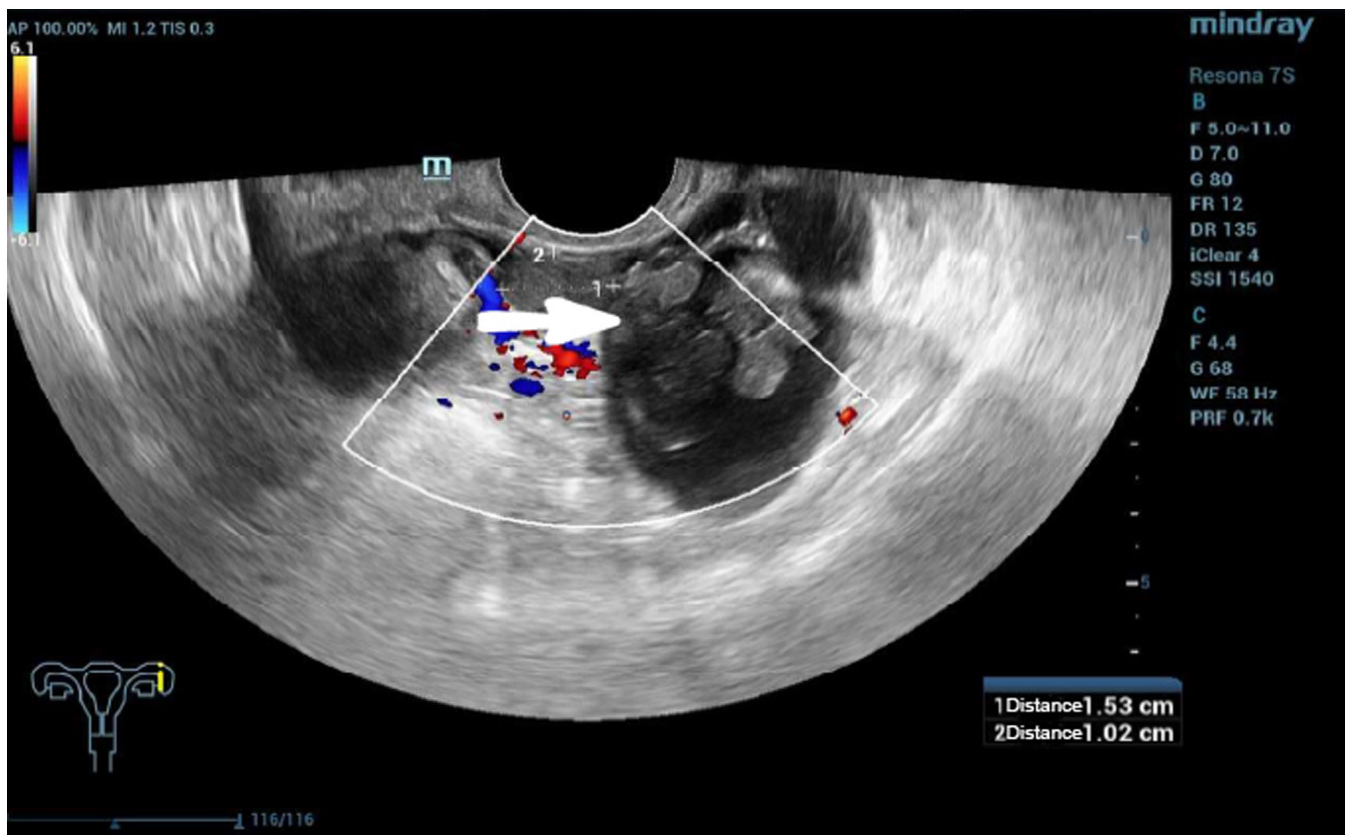


Figure 2. Typical ultrasound image of papillae. The white arrow indicates papillae of serous papillary adenofibroma.

displaying lesion characteristics (Table II). Specifically, MRI more accurately identified well-defined borders (83 vs. 69%), cystic components (83 vs. 62%) and papillae (17 vs. 15%).

Pathological characteristics. Overall, Ki-67, ER, PR, Her-2, BRAF, p53 and WT-1 were tested to determine hormone sensitivity and their association with malignancy of SPAF and prognosis of patients. The IHC images for all the indicators can be found in Figs. 4 and S1. SPAF appeared to be sex hormone-sensitive, as most slices were positive for ER (12/13), PR (13/13) and Her-2 (10/13) (Fig. 4). Low expression of Ki-67, p53 and WT-1 was also observed in the slices, as most of the expressions of Ki-67 (9/13) and p53 (13/13) were no more than 1% or negative (Table III).

Discussion

In the present study, the clinical, laboratory and imaging characteristics of SPAF were summarized and certain molecular markers were determined in SPAF slices. Certain limitations in ordinary examinations were observed but hormone sensitivity of SPAF was also found. Ultrasound is more commonly used due to its low cost and wide availability compared to MRI. However, numerous previous studies have validated that MRI is more effective than ultrasound in detecting SPAF, such as in our cases (4,14).

Benign adnexal tumors are usually asymptomatic and most are incidentally discovered. The main aim of preoperative examination is to exclude the possibility of malignancy.

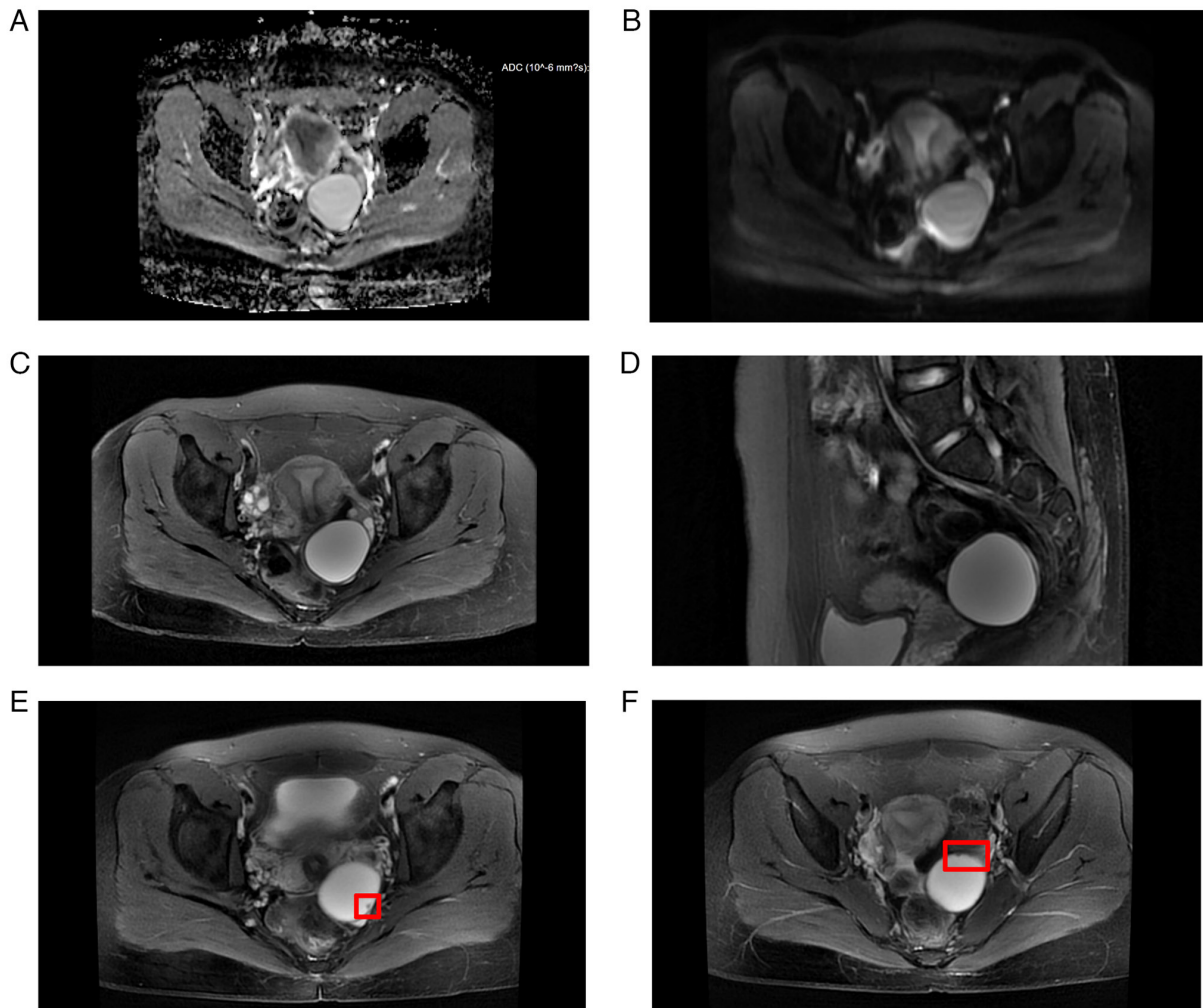


Figure 3. Magnetic resonance imaging appearance of serous papillary adenofibroma in various phases. (A) Transverse section in apparent diffusion coefficient phase. (B) Transverse section in diffusion-weighted imaging phase. (C) Transverse section in T2 phase. (D) Sagittal plane in T2 phase. (E) Transverse section in T2 phase with enhancement from one slice level (red rectangle shows spotted protrusion that is likely to be papillae). (F) Transverse section in T2 phase with enhancement from another slice level (red rectangle shows another spotted protrusion that is likely to be papillae).

However, >10% of patients with benign adnexal lesions still undergo surgery (15). SPAF is a rare benign adnexal tumor that often mimics malignancies. In the present study, it was found that SPAF is difficult to distinguish from other types of ovarian cysts. Therefore, it is important to differentiate it using imaging methods. Sonography and MRI are the most common technologies used in gynecological practice. According to the present results, SPAF shows a cystic or cyst-solid appearance with papillary projections on ultrasound imaging. Generally, these appearances are considered to be signs of malignancy. However, in those with positive ultrasound results, 8 of 11 patients showed a unilocular cyst appearance, which usually represents benign lesions (16). Owing to the limitations of ultrasound, MRI is another radiological examination used for more accurate visualization. A low T2 signal is characteristic of SPAF on MRI because of the fibrous components in the solid part. However, SPAF showed a high T2 signal without solid components. Typically, these signals represent simple fluid. This may have been due to the early stage of SPAF in the patients of the present study. By contrast, CT can visualize nearby organ invasion more clearly. In the present study, it was found that SPAF can appear at either a high or low intensity on

CT scans, making it difficult to diagnose. Therefore, MRI is of significant value in preoperative diagnosis. However, radiologists and gynecologists must also consider the cyst stage. Due to limited published studies, it was only possible to try and predict certain MRI features of SPAF. A serous adenofibroma is a cystic lesion with a regular wall. SPAF should show unilocular or multilocular cysts with solid parts and protrusions on the walls. The present results also confirmed the presence of SPAF papillae on MRI. Further research is needed to distinguish SPAF from other gynecological malignancies.

To our knowledge, no previous study has focused on sex hormone and carbohydrate antigen testing in patients with SPAF. Of note, in the present study, it was found that 3 of 9 patients had elevated PRL levels. PRL is a pivotal molecule associated with the survival and progression of gynecological cancers. Anti-estrogen therapy is a widely applied strategy for the control of numerous gynecological cancers, such as breast, ovarian and endometrial cancers. However, studies have shown that PRL can activate ER- α via p21-activated kinase 1, circumventing the effects of anti-estrogen therapy (17). Of note, it was found that those patients with high PRL levels had high expression of ER and PR, two of which were also

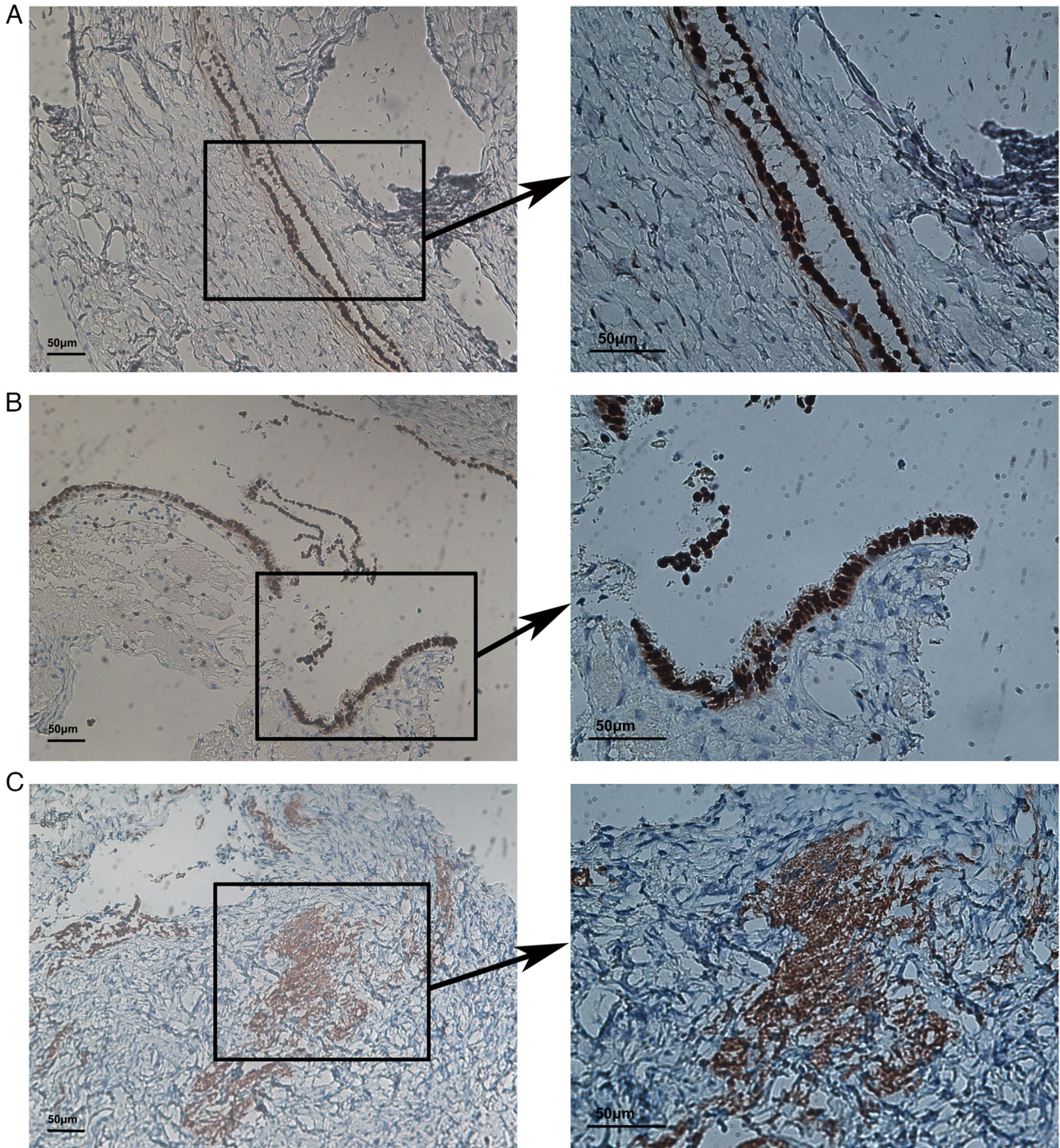


Figure 4. Representative immunohistochemistry images. Strong positivity was encountered for (A) estrogen receptor, (B) progesterone receptor and (C) human epidermal growth factor receptor 2. The right-hand panel shows magnified windows from the left-hand panel (scale bars, 50 μ m).

Her-2 positive. In addition, patients with normal PRL levels failed to achieve an accurate diagnosis of SPAF, particularly in terms of frozen-section pathology. However, patients with elevated PRL levels can be definitively diagnosed. Therefore, PRL expression is likely associated with the pathological appearance and hormone sensitivity. There is evidence to demonstrate a connection between PRL and gynecological malignancies. PRL can phosphorylate STAT3/STAT5 and promote ovarian cancer cell migration and colony formation, and high PRL receptor (PRLR) expression is associated with poor prognosis of ovarian cancer (18). PRLR was also found

to be co-expressed with ER and to promote the metabolism of HeLa cells. However, the exact effect of PRL has yet to be determined. Due to the small sample size of the present study, it is necessary to increase the sample size to evaluate the role of PRL in the development of SPAF.

Ki-67 and BRAF are two common oncogenes that are involved in cell proliferation. As a typical marker of genital tract tumors, Ki-67 usually represents cell proliferation and is used for risk evaluation (19). Clinically, Ki-67 expression can help predict the prognosis of patients with numerous cancer types (20). BRAF is an oncogene that encodes the

Table III. Immunohistochemistry results.

Patient ID	Ki67 (nuclear)		ER (nuclear)		PR (nuclear)		P53 (nuclear)		BRAF (nuclear+cytoplasm)		WT-1 (nuclear)		Her-2 (membrane + cytoplasm)	
	% Stained cells	S.I.	% Stained cells	S.I.	% Stained cells	S.I.	% Stained cells	S.I.	% Stained cells	S.I.	% Stained cells	S.I.	% Stained cells	Membrane staining integrity
1	1	90	2+	2+	95	3+	-	90	1+	+	90	Incomplete	2+	
2	<1	60	2+	2+	80	2+	-	10	1+	+	-	-	-	
3	1	80	2+	2+	95	3+	1	-	-	+	90	Incomplete	2+	
4	2	90	2+	2+	95	3+	1	80	1+	+	90	Incomplete	1+	
5	1	90	2+	2+	95	2+	1	80	1+	+	90	Incomplete	1+	
6	2	80	2+	2+	95	3+	1	80	1+	+	80	Incomplete	1+	
7	<1	95	2+	2+	90	3+	1	-	-	+	80	Incomplete	2+	
8	1	95	2+	2+	90	3+	1	80	1+	+	90	Incomplete	1+	
9	<1	90	2+	2+	90	3+	-	60	1+	+	-	-	-	
10	-	10	1+	1+	60	2+	-	10	1+	+	-	-	-	
11	2	90	2+	2+	90	3+	1	90	1+	+	30	Incomplete	1+	
12	2	95	3+	3+	30	2+	1	90	2+	+	<10	Complete membrane positive	2+	
13	<1	90	2+	2+	95	2+	1	50	1+	-	70	incomplete	1+	

The symbol ‘-’ indicates negative staining. % Stained cells, percentage of stained cells; S.I., staining intensity; ER, estrogen receptor; PR, progesterone receptor; WT-1, Wilms’ tumor protein 1; Her-2, human epidermal growth factor receptor 2.

B-Raf protein and is expressed in several types of tumor (21). The present results showed that SPAF tumors had low Ki-67 and BRAF expression levels. This indicates that SPAF may not be aggressive. Mutations in KRAS, BRAF and Her-2 are thought to be markers of low-grade serous carcinoma (22). In the present study, SPAF showed high expression of Her-2. Therefore, more attention should be paid to diagnosis and prevention. The treatment of gynecological malignancies is complex and expensive. Usually, doctors use comprehensive combination therapy to control malignancy progression. Therefore, early intervention is necessary, particularly in those patients with Her-2 mutation. Low expression levels of p53 and WT-1 indicate a favorable prognosis in patients. Mutations in p53 are caused by multiple cellular stresses and are associated with high-risk tumors (23). WT-1, at the same time, is also a classical marker for cancers in several tissues. To identify risk factors and prevent SPAF recurrence in clinical practice, the present results suggest that hormone therapy may be promising. Patients seem to have hyperestrogenaemia and hyperprolactinemia. IHC staining also showed high expression of ER, PR and Her-2 in the SPAF tissues. Control of sex hormone intake and anti-sex hormone therapy may be applied to patients who were already diagnosed with SPAF and underwent surgery.

Nevertheless, the present study has limitations, primarily its small sample size. It is therefore recommended that future large-scale or multi-center studies are performed. Building on these findings, it may be worthwhile to establish a relationship between MRI features, hormone levels (particularly PRL) and disease progression in patients with SPAF and develop an integrated MRI-hormone diagnostic algorithm to optimize preoperative diagnostic accuracy. Furthermore, prospective studies may clarify the impact of postoperative anti-sex hormone therapy on prognosis. Finally, while IHC staining is necessary for identifying molecular markers, its results are affected by multiple factors and are subjective based on observers. Western blot analysis or PCR may be required in future applications to validate results and improve standardization if possible (24).

In conclusion, SPAF is a benign tumor that mimics malignancy. Owing to its rarity, SPAF tends to be diagnosed postoperatively. Radiologists may be advised to determine certain characteristics of SPAF, particularly on MRI imaging. High sex hormone levels may be another indication of SPAF. Because SPAF shows low malignancy, more attention should be paid to its prevention and early diagnosis. IHC staining results suggest that SPAF is sensitive to sex hormones. This can be used by gynecologists to help reduce recurrence in patients.

Acknowledgements

The authors acknowledge the clinical data support of the Second Affiliated Hospital Zhejiang University School of Medicine (Hangzhou, China).

Funding

This work was supported by Zhejiang Traditional Chinese Medicine Administration (grant no. 2024038810).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, experimental result interpretation, data collection and analysis were performed by XZ and CY. YL and XL checked and confirmed the authenticity of the raw data. The first draft and final edit of the manuscript were prepared by XZ and all authors commented on previous versions of the manuscript. XW edited all tables and figures. YL and XL searched relevant articles and references. ZY directed the data analysis. LW revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Second Affiliated Hospital Zhejiang University School of Medicine (Hangzhou, China; approval no. 20231165). Based on specific criteria, the Ethics Committee granted a formal waiver of informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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