

## Original Article

# Clinicopathological characteristics of ovarian low-grade malignant Wolffian adnexal tumor: a case report

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**Abstract:** Wolffian adnexal tumor (WAT) is a rare tumor with low potential of malignancy. Most cases appear to behave in a benign fashion, but recurrence and metastasis has also been reported. Malignant ovarian WAT is exceptionally rare. Here we report one case of WAT, in order to explore its clinicopathological/immunohistochemical characteristics, and differential diagnosis. The patient is a 63-year old female who was found to have pelvic mass by census, and received laparoscopic bilateral oophorectomy, during which hyperplasia was seen in her left and right ovaries. Gross examination showed that the tumor was a partially cystic mass (5 × 3.8 × 2.5 cm) in her left ovary, and 6 × 5 × 1.5 cm size in the right. Microscopic examination showed the tumor cells were small tubular, lined with columnar epithelial cells of the gland, with 4~5 mitotic/10 high-power fields. The results of immunohistochemistry showed that vimentin, PAX-8, EMA, E-cadherin, MC were positive, and CgA, Syn, calretinin etc. were negative. The Ki67 proliferation index was 30%. Based on the clinicopathological and immunohistochemical characteristics, the tumor was diagnosed as WAT, which should be differentiated from other gynecological tumors.

**Keywords:** Ovarian Wolffian adnexal tumor, low-grade malignant, immunohistochemistry

## Introduction

Wolffian Adnexal tumor (WAT) is a relatively rare type of cancer, which was first reported in 1973 by Kariminejad and Scully [1]. So far, there are over 70 cases reported in the literature [2], mostly occurring in the broad ligament and mesosalpinx, but rarely in the ovary, retroperitoneal Adnexal paravaginal [3]. The tumor is generally considered benign lesions [4], but more than twenty cases of malignant WAT with recurrence or metastases have been reported, with one case in China [5], among which, only 4 cases occurred in ovary (Table 1). Here, we reported a case of low-grade malignant WAT derived from ovarian tissues.

## Materials and methods

### Clinical data

Here we report a 63-year old female with the history of 1 time of full-term delivery, no premature delivery, 1 time of miscarriage, and one child. Two years ago, she was found to have pelvic mass by census, which was considered to

be benign ovarian tumors, the patient received conservative medical treatment but no obvious efficacy. On October 7, 2014, she visited the outpatient department of our hospital. The B-type Ultrasound examination showed that there were cysts on both sides of her uterus, which may derive from uterine accessories (left side 3.8 × 4.8 × 4.5 cm, right side 4.3 × 5.5 × 5.3 cm). The serum CEA, CA125, CA199, and AFP were normal, and there was no abnormal vaginal bleeding. On October 21, 2014, the patient was admitted, and received laparoscopic bilateral oophorectomy, during which hyperplasia was seen in her left and right ovaries. The cyst in her left ovary was 4 cm in diameter, and the cyst in her right ovary was 5 cm in diameter. Both cysts contained clear liquid inside. The uterine and fallopian tubes at both sides had normal appearance.

### Methods

Specimens were fixed in 10% formalin, dehydrated, and embedded in paraffin for 4 μm sections. After HE staining, the slides were obser-

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**Table 1.** Occurs in the ovaries WAT clinical and pathological features

Reference	The number of cases	Age (yr)	Size (cm)	Shape	Clinical manifestations	Pathological features	Prognosis	Property			
Young RH [13] et al 1983	9	28-58	2-20 in diameter	Four cases occurred in the left and right five cases, two cases of the unknown; 5 cases of solid, six cases of cystic	Some patients have clinical manifestations (abdominal distension, abdominal pain, frequent urination or vaginal bleeding), some patients with no obvious discomfort	Cell atypia, mitotic no obvious	The average follow-up of 5 years with no recurrence and metastasis				
	1	52	8 in diameter						Cellular atypia, mitotic 13/10 HPF	8 years after the death of lungs metastasis	Malignant
	1	64	8 in diameter						Cellular atypia, mitotic 16/10 HPF	Lost	Malignant
Inoue H [14] et al 1995	1	64	10 * 7 * 3	Right ovary, solid, smooth surface	Vaginal bleeding, abdominal distension, increased estrogen (return to normal after surgery), accompanied by endometrial hyperplasia	Reticular formation Tubular structure	Follow-up of 14 months no recurrence and metastasis				
Ramirez PT [9] et al 2002	1	71	16 * 12 * 5	Multiple solid nodules	No obvious discomfort	Omentum, mesentery metastasis	1 year after liver planting	Malignant			
Deen S [15] and others 2007	1	81	18 * 12 * 8	Right ovary, solid nodules, crisp	CA125 increased bleeding after menopause	Cells without atypia, mitotic 12/10 HPF	7 months after pelvic tumor recurrence	Malignant			
Li F [4] et al 2008	1	87	4.5 * 4 * 2.5	Right ovary, cystic	Endometrial resection found	Polycystic structure with a sheet spindle cell area, cells without atypia, mitotic <1/10 HPF	7-month follow-up no recurrence and metastasis				
Juan [16] et al 2014	1	59	11 * 8 * 6	Left ovary, cystic, capsule contents yellowish liquid, the inner wall of the side of papillary	No obvious Unwell	Tubules and sieve-like structure with part-solid region, cell atypia, no mitotic	Follow-up of 10 months no recurrence and metastasis				
Present case	1	63	5 * 3.8 * 2.5	Left ovary, cystic, capsule contents clear liquid, capsule solid nodules	No obvious Unwell	The tubular structure of the same size, cell medium shaped, mitotic 4~5/10 HPF	3-month follow-up no recurrence and metastasis	Malignant			

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**Figure 1.** The excised cyst. The boundary wall was clear with nodules, size 2 \* 2 \* 1 cm, The sections were grey-white, medium texture. The surface of the cyst was attached to a fallopian tube.

ved under light microscopy, AB/PAS special staining, mesh and immunohistochemical staining. Ventana method was used for immunohistochemistry. The (Roche/Ventana, Benchmark GX) with automatic multi-functional pathology detection system was used for immunohistochemical staining. Antibodies that were used in the study: Calretinin (SP13), CK7 (clone No. OV-TL12/30), CD117 (YR145), CD99 (O13), inhibin- $\alpha$  (R1), MC (HBME-1), P53 (DO-7), WT-1 (WT49), villin (SP145), vimentin (V9), which were purchased from Fuzhou Maixin Biotechnology Limited; CK (AE1/AE3), CK20 (Ks-20.8), CgA (LK2H10 + PHE5), Ki-67 (SP6), ER (SP1), E-cadherin (SPM471), EMA (GP1.4), Syn (SP11), TG (2H11 + 6EG1), and PR (SP2) were purchased from DAKO company; CD10 (56C6), PAX-8 (ZR-1) were purchased from Shanghai Gene Technology Limited. A known positive tissue was used as control.

### Results

#### Gross examination

The bilateral annex was obtained during the surgery. The left ovarian cyst, size 5 × 3.8 × 2.5 cm, had been cut open, the contents already lost, wall thickness 0.2 cm, and the inner wall was smooth. A circumscribed nodule within local was seen, size 2 × 2 × 1 cm, white-grey section, medium texture (**Figure 1**). The right ovarian cyst was of 6 × 5 × 1.5 cm size, 0.2 cm of the wall thickness, containing clear liquid, and of smooth wall. No obvious abnormalities were seen in the tubes.

#### Microscopy

The left ovarian cyst wall was locally lined by flat cells, no cell lining covering most of the area. The nodules between the cyst walls were composed of glandular structures (**Figure 2A, 2B**). The duct shape and size were relatively homogeneous, showing a small number of ducts expanded. The ducts were separated from each other, some fused. There were eosinophilic substance and necrosis in the glandular lumens (**Figure 2C**). The glandular cells were lined with columnar epithelial cells, vesicular nuclei, more clearly visible nucleoli, mitotic 4~5/10 HPF (**Figure 2D**). There was visible fibrous stroma between ducts. The wall of the right ovarian cyst was lined by a small number of flat cells.

#### Immunohistochemistry and special staining

Vimentin (**Figure 3A**), PAX-8, EMA, E-cadherin, MC (**Figure 3B**) were positive; CK (**Figure 3C**), CK7, CD99, ER were focally positive; Ki-67 was 30% positive (**Figure 3D**), CgA, Syn, Calretinin, CK20, P53, Inhibin- $\alpha$ , TG, WT-1, Villin, CD10, CD117, PR were negative. PAS staining: intraluminal red dye was positive (**Figure 4**).

#### Pathological diagnosis

The diagnosis was (left) ovarian low malignant Wolffian adnexal tumor, which was made by our hospital, and confirmed by Shanghai Fudan University Cancer Hospital Pathology consultation.

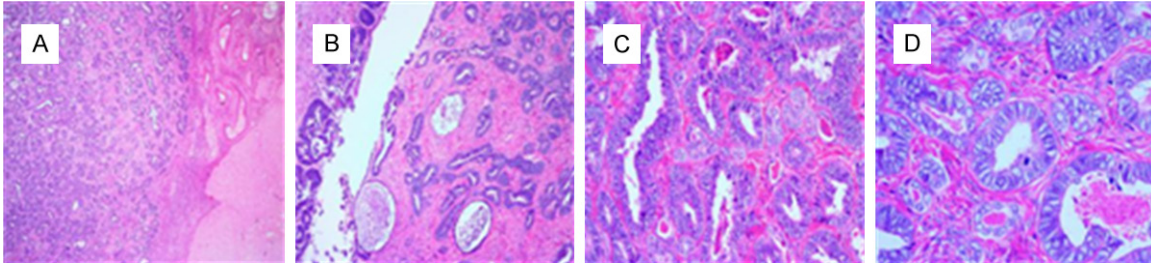
#### Treatment and follow-up

After the diagnosis, patient underwent hysterectomy. The postoperative pathological examination showed no abnormalities. 3-month follow-up showed no recurrence and metastasis.

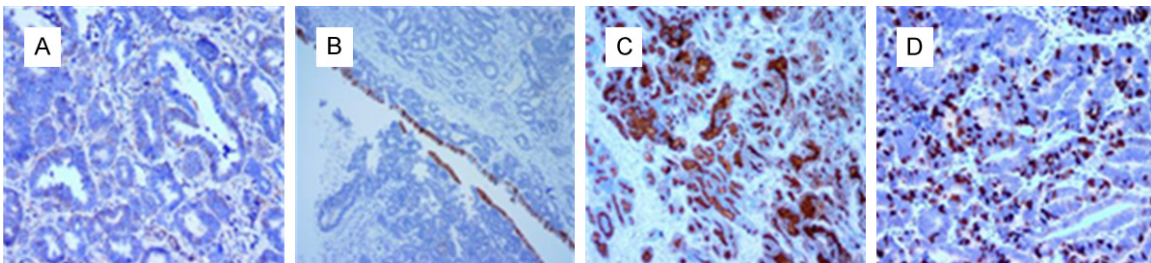
#### Discussion

In 1973, 9 cases of tumor outside of ovary, with special morphology, was first reported [1], These tumors were located in broad ligament or mesosalpinx, the regions rich in the Wolffian duct. At that time these tumors were named "female adnexal tumor of probable Wolffian origin FATWO". No more than one hundred cases have been reported to date. With the development of clinical diagnosis technology, FATWO has been proved to be indeed originated in the

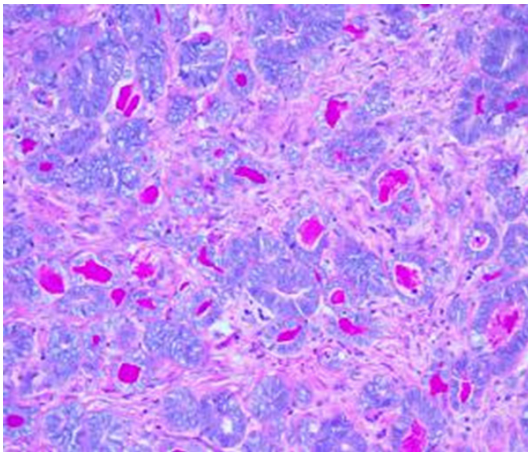
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**Figure 2.** A. The tumor is composed of glandular structures that are relatively homogeneous in shape and size. The glandular structures are independent of each other, with occasional integrations. (HE  $\times$  40). B. There are a few lumen expansions. Fibrous stroma was seen between ducts. (HE  $\times$  40). C. Glandular ducts were lined with columnar cells, moderately abnormal, some nuclear vacuoles, some necrosis was seen in the lumen. (HE  $\times$  200). D. Mitotic was seen (HE  $\times$  400).



**Figure 3.** A. Tumor vimentin positive cells (EnVision  $\times$  200). B. Focal tumor cells CK expression (EnVision  $\times$  100). C. Tumor cells MC expression (EnVision  $\times$  100). D. Tumor cells positive for Ki-67 30% (EnVision  $\times$  200).



**Figure 4.** PAS intraluminal eosinophilic material positive (PAS  $\times$  200).

Wolffian duct. In 2003, WHO officially named it Wolffian adnexal tumor WAT [6], classified as miscellaneous tumors, defined as borderline- or uncertain-biological-behavior tumor.

WAT mostly occurs in middle-aged women, ranging from 13 to 87 years old, with a median age of 50 years [7]. There can be no specific clinical manifestations, which may present with

abdominal pain, bloating, abdominal fluid, vaginal bleeding and other symptoms. The tumor occurs at the sites of tissue distribution of Wolffian duct remnants [8], from the ovary door to 1/3 vagina, along the fallopian tubes mesometrium and the side of the uterus, among which the most commonly seen are in the broad ligament and mesosalpinx, while it is rarely seen in retroperitoneal and near the vagina. Most tumors are unilateral, mainly in the right side rather than the left. In this case, the tumor occurred in the left ovary.

WAT was 0.5-25 cm in diameter, with an average of 6 cm. most tumor surface smooth, with clear boundaries or enveloped. The section was sallow or brown, can be in solid, cystic or cystic-solid. The solid areas may be in leaf shape, texture hard and tough. The tumor may contain serous or gelatinous liquid cysts. In some cases it can present with bleeding and central necrosis.

Microscopic tumor morphology can be varied, can be tubular, cribriform or solid diffused, and several structures can coexist in the same tumor, wherein the tubular and sieve-like struc-



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tures are considered to be the characteristic features [9]. Tubular structure varies in size and shape. Under pressure, the lumen can be crack-like, and can also be staggered with each other. The lumen is lined with low columnar or cubic luminal epithelium, sometimes with high columnar epithelium, and the lumen periphery has clear base membrane-like substance [10]. In the sieve-like structures, there are cysts with varying sizes, which are lined with a single layer of flat or columnar epithelium. The solid structure contains a large number of polygons or spindle cells. The nuclei are oval or round, with homogeneous nuclear chromatin. Single small nucleolus or nucleolus is not obvious. Regardless of the tubular area or solid areas, the tumor cells are not significantly shaped. Mitotic is rarely seen (usually 0 to 3/10 HPF). In the present case, the cystic tumors, tumor microscopic morphological characteristics were different from previous reports. It was mainly composed of glandular structures, duct shape and size relatively homogeneous, some glands showed a small cystic dilatation. The ducts were independently of each other, with occasional fusion, glandular lumens eosinophilic material (PAS positive) and necrosis. The lumen was lined with columnar epithelial cells, and cilia-like structures were seen in partial lumen cavity edge. The cells were moderately shaped, with nuclear vacuoles, and visible clear nucleoli, mitotic 4~5/10 HPF. PAS negative gland was visible between the fibrous stroma.

WAT immune phenotypes reported in the literature vary. Devouassoux-Shisheboran et al [11] summarized 25 cases of WAT, and reported that they all expressed CK and vimentin, 90% expressed calretinin, and 68% expressed inhibin- $\alpha$ . It has been reported that WT1 and tumor cells may express CD99 [12]. CD117, E-cadherin-positive WAT was also reported. There is some overlap of immune phenotypes between WAT and epithelial tumors, sex cord stromal tumors. It is generally thought that immunohistochemistry has no significance in the diagnostics of WAT. In the present case, the microscopic morphology of the tumor (isolated lumen structure, relatively homogeneous shape and size) differs from the previously reported WAT. Combining the immunohistochemical results (diffuse expression of EMA, vimentin, PAX-8, E-cad and MC; Bureau stove express CK, CK7, CD99 and ER; not expressing CgA,

Syn, CK20, inhibin- $\alpha$ , calretinin, TG, etc.), the diagnosis of carcinoid tumors, epithelial tumors could be ruled out, and finally it was diagnosed as WAT.

WAT is easily misdiagnosed, which should be differentiated with endometrial adenocarcinoma, granulosa cell tumor, support-Leydig cell tumors. (1) endometrial adenocarcinoma: this tumor has obvious atypia and mitotic cells, primarily in the ovaries, in the present case; this can be ruled out by immunohistochemistry. (2) granulosa cell tumors: these tumors can secrete high levels of estrogen, patients often present with endocrine disorders. Granulosa cell tumors occur in the ovary, the tumor cell nucleus is bean-like, with obvious nuclear grooves, visible Call-Exner bodies. These special structures are useful in differential diagnosis. (3) Support-Leydig cell tumor: the tumor generally occurs in the ovary, microscopic tumor cells seen Ledig, visible heterologous ingredients. In addition, patients often present with high androgen levels. (4) Source mesothelial tumors: these tumors need to be differentiated with cribriform type WAT. Immunohistochemistry may help the diagnosis. The combination of histology tumors mesothelial tumors may exclude. (5) Carcinoid: carcinoid is easy confused with WAT tubular structure, but often with teratoma merger carcinoid. Immunohistochemistry may also provide some characteristic features for diagnosis. In this case, the morphology of the tumor is similar to that of carcinoid, but no teratoma component was seen around the tumor, The immunohistochemistry of CgA, Syn, TG was negative, which can exclude the diagnosis of carcinoid tumors.

WAT occurring in the ovary is relatively rare In 1983, Young [12] et al reported 11 cases, which is so far the largest number of cases. There was one case in China, which was benign as previously reported. In order to further investigate the clinical and pathological features of ovarian WAT, in this paper, we analyzed the 16 patients of ovarian WAT that were previously reported in the literatures (**Table 1**). The patients were 28-87 years old, with ovarian WAT that occurred mostly in the unilateral ovary, and mostly in the right. The tumor was 2-20 centimeters in diameter, solid or cystic. Patients may present with no obvious clinical manifestations, such as abdominal pain, bloating, fre-

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quent urination, vaginal bleeding and other symptoms. WAT occurs generally considered independent of hormone secretion, Inoue [13] reported one case of WAT that occurred to the right ovary had significantly increased expression of estrogen, which returned to normal after surgery. The follow-up of these 16 cases of ovarian WAT showed recurrence and metastasis in 3 cases. These three cases shared the feature of a large tumor size, more nuclear mitotic. In this article, we reported one case of ovarian WAT glandular, in which necrosis, cellular atypia, mitotic were seen inside the glandular cavity. Long-term follow-up may be needed to determine the prognosis.

WAT in a very long period of time was considered a kind of benign lesions, however, it has been reported that the tumor may relapse and metastasis. Sivridis et al [16] proposed diagnostic criteria for malignancy WAT: larger tumors (diameter > 10 cm), rich in cells, coated nodular projections, rupture, bleeding necrosis, as well as planting and metastasis. Heatley [17] reviewed 31 literatures, of which the follow-up data in 63 patients were analyzed. The results showed: 50 patients were alive and healthy, 7 patients relapsed, 3 patients died the other three cases patients died of other causes. Site of tumor recurrence was mostly in abdominal, pelvic, distant metastasis to the liver, lungs, and even can be transferred to the spleen, appendix. The postoperative recurrence time was largely 1-8 years.

Unilateral oophorectomy is generally performed in WAT patients, with close postoperative follow-up. The efficacy of radiotherapy and chemotherapy is poor. Atallah et al [18] reported one case of recurrence and metastasis after pregnancy, suggesting that WAT may be hormone-dependent, and hormone therapy was thus proposed to have a role in the control of tumor recurrence. Syriac et al [19] the reported 1 case of tumor recurrence after three years of molecular targeted therapy. The efficacy has not been set yet. In the present case, the tumor size was 2 × 2 × 1 cm, clear boundaries, microscopic tubular structures, necrosis within the glandular cells with moderate atypia, mitotic 4~5/10 HPF, Ki-67 proliferation index was 30%, the diagnosis of low-grade WAT, now with total hysterectomy. The patient is currently under follow-up.

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### Disclosure of conflict of interest

None.

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