

Ovarian Mucinous Tumor with Mural Nodules of Anaplastic Carcinoma: A Clinicopathological Analysis of Three Cases Report and Review of Related Literature

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Case Report

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Abstract

Background:

Anaplastic carcinoma mural nodules presenting in ovarian mucinous cystic tumors are very rare. Here, we reported clinicopathological, immunohistochemical and molecular features of 3 such cases, and reviewed the related literature.

Case presentation:

The expression of pan-cytokeratin (CK) in the mural nodules of all three patients supported the diagnosis of mural nodules of anaplastic carcinoma. Immunohistochemical staining showed wild-type expression of p53 in the mural nodules and mucinous epithelium of Cases 2 and 3, while Case 1 was negative for the p53 mutation. The synchronous expression of p53 in epithelia and mural nodules suggested that mural nodules might be homologous with mucinous adenocarcinoma and might be the result of dedifferentiation of mucinous adenocarcinoma. In the sarcomatoid region of Case 1, p53 was wild-type in spindle cells and multinucleated giant cells in the background. In Case 3, a broad-based serrated adenoma of the appendix was also found. Therefore, exons of tumor-related genes were detected by high-throughput next-generation sequencing (NGS). Missense mutations of *PIK3CA* and *PTEN* were found, but no germline mutations were detected.

Conclusions:

In young patients with sarcomalike mural nodule (SLMNs) morphology, pathological analysis is recommended to avoid overlooking the existence of malignant mural nodules. Serrated lesions occurred in the appendix and ovarian mucinous tumor simultaneously, but no germline mutations were detected by NGS, indicating this was a sporadic case.

Background

Primary ovarian mucinous cystic tumors, whether benign, borderline, or malignant, may be associated with mural nodules of various types, including true sarcomas, sarcoma-like mural nodules, anaplastic carcinomas, carcinosarcoma, mixed nodules and leiomyomas [1, 2]. However, cases of mucinous cystic of ovary with mural nodules are rare and the histogenesis of the mural nodules in ovarian mucinous cystic tumors is unclear. In this study, we reported three ovarian mucinous cystic tumor contained solid nodules of anaplastic carcinoma in their walls and evaluated the clinicopathological analysis of three cases. To our know, there are only a few reports of mucinous ovarian tumors associated with foci of anaplastic carcinoma.

Case Presentation

Materials

We evaluated three cases of ovarian mucinous cystic tumor with anaplastic carcinoma mural nodules treated at the Pathology Department of Shanxi Cancer Hospital (China) between 2015 and 2020. Clinical data were obtained from the medical records.

Methods

The specimens were fixed with 4% neutral formaldehyde solution, dehydrated and embedded in paraffin. Sections (4 µm thickness) were prepared and processed for routine hematoxylin-eosin (HE) staining and light microscope observation. The diagnosis was confirmed by senior general practitioners.

Immunohistochemical staining was performed on a Roche benchmark Ventana automatic detection platform. The following were used as primary detection antibodies: CK (clone number: AE1/AE3, dilution ratio: 1:200), vimentin (clone number: UMAB159, dilution ratio: 1:1500), Pax-8 (clone number: OTI6H8, ready to use), PTEN (clone number: D4.3, ready to use), Ki67 (clone number: UMAB107, dilution ratio: 1:500) (all purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., p53 (clone number: BP-53-12, dilution ratio: 1:600), ER (clone number: SP1, dilution ratio: 1:200), and PR (clone number: SP2, dilution ratio: 1:100), ini-1 (clone number: 25, ready to use) (all purchased from Gene Technology (Shanghai) Co., Ltd.). Abnormal expression of p53 was defined as > 70% of the nuclei found to be strongly positive or totally negative by immunohistochemical staining. Peripheral blood samples were collected and analyzed using a next-generation sequencing method at Jianwei Medical Laboratory Co., Ltd.

Results

Clinical cases

Clinical Case 1 was a 25-year-old woman who presented with a conscious abdominal circumference increase for two weeks. Ultrasonic imaging showed a huge abdominal cavity cystic mixed mass with a thick cystic area and septum. The following tumor markers were detected before resection: carcinoembryonic antigen (CEA) 1.73 µg/L, alpha fetoprotein (AFP) 2.66 µg/L, cancer antigen (CA)125 26.66 U/ml, and CA199 21.66 U/ml. The left salpingo-oophorectomy were performed. The tumour proved to be malignant on frozen section examination, but the patient refused to future the right salpingo-oophorectomy, hysterectomy and omentectomy, and chemotherapy. Twelve months after operation, the patient was died due to the tumour recurrence and pleural metastasis.

Case 2 was a 60 years old woman who presented with lower abdominal distension for more than two weeks. B-mode ultrasound showed multilocular cystic solid masses in the pelvic cavity. The following tumor markers were detected: CEA 0.72 µg/L, AFP 0.63 µg/L, CA125 1.50 U/ml, and CA199 5.40 U/ml. Bilateral salpingo-oophorectomy, appendectomy and omentectomy were performed. The postoperative was uneventful. The patient was died of other cause 18 months after operation.

Case 3 was a 55-year-old woman who presented with dull abdominal pain 12 years after a hysterectomy. B-mode ultrasound showed a cystic solid mass on the right side of the pelvic cavity with a clear

boundary. The following tumor markers were detected: CEA 4.00 µg/l, CA125 142.07 U/ml, and CA199 524.60 U/ml. The right ovary was performed frozen section examination and proved to be malignant. The patient received multiple-drug chemotherapy (three cycles of Paclitaxel and Carboplatin). The woman is alive and well without evidence of tumor recurrence.

The detail clinicopathological features of these three cases have been boiled down in Table 1.

Table 1
Clinicopathological features of three cases of ovarian mucinous tumors

Case	Age(year)	Mucinous Tumor	Size of Nodule (cm)	Nodule Type	FIGO stage	Prognosis
1	25	MA	4×4×4	SAAC	Ic	DT(12 months)
2	60	BMC	3×3×3	AC	Ia	DT(18 months)
3	55	MA	1×1×1	AC	IIIc	TFS

MA: Mucinous adenocarcinoma; BMC: borderline mucinous cystadenoma; SAAC: Sarcoma like and anaplastic carcinoma; AC: Anaplastic carcinoma; DT: Death from tumor; TFS: Tumor free survival

Pathological features

Microscopic findings

In Case 1, the left ovary specimen consisted of single cyst measuring 18 cm × 17 cm × 2 cm that were gray with a smooth external surface, and it had been opened clinically. Part of the inner wall was smooth and the wall thickness was approximately 0.5–1.0 cm. Several grey or dark brown mural nodules projecting into the cyst cavities measuring with a diameter of 1–4 cm.

In Case 2, the right ovary specimen consisted of multilocular cystic measuring 11 cm × 8 cm × 2 cm that were gray with a smooth external surface, and it had been opened clinically. The inner wall was smooth. The wall thickness was approximately 0.1–0.2 cm, with mural nodules (diameter 3 cm) attached to some areas. In cross-section, the protrusion appeared gray/yellow and was brittle.

In Case 3, the size of the right ovary was 12 cm × 10 cm × 2 cm, the surface was smooth, it had been opened clinically. In cross-section, the mass was cystic, with a wall thickness of approximately 0.2–1.0 cm. In some areas, multiple vesicles were found in the wall of the cyst (diameter 0.5–4 cm) containing light yellow liquid. Two gray/white nodules (diameter 0.8–1.0 cm) were observed on the cyst wall. In cross-section, the nodule appeared gray-yellow and brittle. The appendix (length 3.5 cm; diameter 0.5 cm) was resected simultaneously.

Microscopic examination

In Case 1, the wall of the cyst was lined with mucinous columnar epithelium. The nucleus was obviously heteromorphic, showing complex papillary branches protruding into the cavity, and swelling interstitial infiltration in the focal area. Part of the cyst wall was thickened and spindle cell nodules were scattered in the wall. Some nodules were composed of spindle cells, multinucleated giant cells and histiocytes. Massive levels of hemorrhage, necrosis and hemosiderin deposition were found in the nodules. Multinucleated giant cells with abundant eosinophilic cytoplasm were detected with an osteoclast-like appearance (Fig. 1A). Some of the nodule spindle cells showed infiltrative growth, mixed with mucinous epithelium. The nucleus was obviously heteromorphic and nucleoli were visible. Mitosis was clearly observed (approximately 25/10 HPF) including pathological mitosis (Fig. 1B).

In Case 2, the cystic wall was lined with mucinous columnar epithelium. The nucleus was slightly heteromorphic, and some of showed a micropapillary structure. The spindle and oval cells distributed in the fibrous interstitium of the cystic wall exhibited a fish bone structure. The nuclei were obviously heteromorphic, with nucleoli, mitotic figures (> 15/10 HPF), and pathological mitosis (Fig. 1C).

In Case 3, the cystic lesions were lined with mucinous plasma epithelium. The nuclei were heteromorphic, and the interstitial nuclei were loose and edematous. Two well-defined nodules were observed, and a nodule (diameter approximately 0.8 cm) was infiltrated with atypical mucinous glands. Heterotypic spindle cells were seen in another nodule (1 cm in diameter), with mitotic figures (approximately 7/10 HPF) (Fig. 1D).

Immunohistochemical results (see Table 2).

Table 2
Immunohistochemical Results

	Case 1		Case 2		Case 3	
	epithelium	nodule	epithelium	nodule	epithelium	nodule
AE1/AE3	Positive	Positive	Positive	Positive	Positive	Positive
Vim	Negative	Positive	Negative	Positive	Negative	Positive
Ki67	70%	80%	30%	80%	40%	70%
ER	Negative	Negative	Negative	Negative	Negative	Negative
PR	Negative	Negative	Negative	Negative	Negative	Negative
Pax8	Focally positive	Negative	Positive	Positive	Positive	Positive
P53	Mutation negative	Mutation negative	Wild positive	Wild positive	Wild positive	Wild positive
PTEN	Positive	Positive	Positive	Positive	Negative	Negative
CK7	Positive	Positive	Positive	Positive	Positive	Positive
CK20	Negative	Negative	Positive	Negative	Negative	Negative

Pathological diagnosis

Case 1 was diagnosed as ovarian mucinous adenocarcinoma with sarcomalike and anaplastic carcinoma mural nodules, without omentum involvement. The ovarian mucinous adenocarcinoma cells can be found in the ascites. The patient was classed as FIGO stage IC.

Case 2 was diagnosed as borderline mucinous cystadenoma of the ovary with mural nodules of anaplastic carcinoma. No lesions were found in the omentum, lymph nodes and appendix. The patient was classed as FIGO stage IA.

Case 3 was diagnosed as ovarian mucinous adenocarcinoma with anaplastic carcinoma, mural nodules and broad-based serrated adenoma of the appendix. Tumors were found in the omentum and the opposite side of the ovary. The patient was classed as FIGO stage IIIC.

NGS analysis of Case 3

No germline mutation was found, but missense mutations of *PIK3CA* and *PTEN* were identified. No mutations were found in the *KRAS*, *p53*, *NTRK1*, *NTRK2*, *NTRK3*, *JAK1*, *JAK2* and *ALK* genes (see Table 3).

Table 3
Analysis of point mutation and insertion deletion variation

Gene	Mutation type	Exon	Base mutation	Amino acid	Frequency	COSMIC ID
PIK3CA	Missense	exon10	c.1616C > G	p.P539R	0.67%	759
PTEN	Missense	exon7	c.520T > G	p.Y174D	2.14%	28897

Discussion

Ovarian mucinous tumors with mural nodules are rare. Such mucinous epithelium can be benign, borderline or malignant. Although there have been sporadic reports of malignant mural nodules, such as clear cell carcinoma, carcinosarcoma, and sarcoma, the most common type of mural nodular malignancy is anaplastic carcinoma [3]. The mural nodules of anaplastic carcinoma can be divided into three types: rhabdomyoid, spindle cell-like and pleomorphic [2, 4]. The three cases of anaplastic carcinoma in our report were spindle cell-like.

Case 1 was a young woman with SLMNs. In some areas, spindle cells showed infiltrative growth, and immunohistochemical staining showed diffuse expression of AE1/AE3, p53 was negative for mutation type (Figs. 2A and 2B). Matias-Guiu et al. [5] proposed that cytokeratin immunohistochemical staining should be used to distinguish SLMNs and anaplastic carcinoma mural nodules. CK staining was negative or focal positive in SLMNs, while strong positive diffuse staining was detected in anaplastic carcinoma nodules. The heterogeneous expression of AE1/AE3 and p53 in Case 1 (Figs. 2C and 2D) suggested that there were two components in the mural nodule. Therefore, the patient was diagnosed as mucinous adenocarcinoma with sarcomalike and anaplastic carcinoma mural nodules. In a literature review, Shao et al. [6] reported that most benign SLMNs are associated with anaplastic carcinoma mural nodules. Case 1 was young and the anaplastic carcinoma was spindle-shaped, which is not easy to distinguish from spindle cells in SLMNs, making this very easy to overlook in the diagnosis process. Therefore, it is necessary to take sufficient samples for careful observation.

The differential diagnosis between SLMNs and sarcomatous or anaplastic carcinoma mural nodules is generally considered to be particularly important. SLMNs have a good prognosis because of their inert clinicopathological characteristics. The formation of SLMNs may be the result of differentiation of undifferentiated mesenchymal cells beneath the mucinous epithelium into epithelial cells, elicited by some stimulation, for example, intramural hemorrhage or cyst contents. Zheng et al. [3] reported that the proliferation of multinucleated giant cells was mostly located between the basement membrane of the mucous epithelium and the stromal cells in the bleeding area of the cystic wall in sarcomalike cases with anaplastic carcinoma. It was suggested that the formation of SLMNs might be the result of differentiation of undifferentiated stromal cells beneath the mucous epithelium under external stimulation. However, the latest research on mural nodules showed that there were tumor cell groups with abnormal expression of p53 and MTAP in SLMNs, and molecular detection suggested that SLMNs are not a benign reactive process and all mural nodules in mucinous ovarian tumors should be regarded as

potentially malignant neoplasms. Therefore all mural nodules in mucinous ovarian need to be thorough sampling and rigorous clinical correlation to exclude extraovarian spread [3, 7]. Based on the results of HE morphological evaluation and molecular detection of the former, the molecular detection results may be closer to the nature of mural nodules. Therefore, SLMNs may not be the result of reactive process of mucinous tumors, but the clonal derivatives of ovarian mucinous tumors.

Case 1 refused to expand the scope of the operation and postoperative chemotherapy. Pleural thickening and pleural effusion were found 11 months after the operation. Pleural biopsy showed adenocarcinoma and immunohistochemistry showed metastasis. Adenocarcinoma cells were found in pleural effusion and ascites, and the patient died 12 months after surgery.

In Case 1, both mucinous adenocarcinoma and anaplastic carcinoma nodules were negative p53 mutations, while in Cases 2 and 3, p53 was wild-type (Figs. 2E and 2F). The synchronous expression of p53 in epithelia and mural nodules suggested that mural nodules may be homologous with mucinous tumors, which is the result of dedifferentiation of mucinous tumors and tumor lesions. This conjecture is consistent with reports by Desouki et al. [8] and Zheng et al. [3]. Shao et al. [6] and others also speculated that the mural nodules of anaplastic carcinoma may be the result of dedifferentiation of mucinous tumors, in which p53 mutation plays a key role. Chapel et al. [7] reported that only 1 of 13 patients had p53 mutations in mural nodules, while no mutations were detected in mucinous tumors. There were eight cases with the same p53 mutation, indicating that p53 mutation does not play a key role in the occurrence of mural nodules. Although the immunohistochemical expression of p53 was not completely consistent with the results of molecular detection, no p53 mutation was found in the three cases of mural nodules of anaplastic carcinoma reported here. NGS analysis of Case 3 also confirmed the absence of mutations p53.

Case 3 was diagnosed as ovarian mucinous tumor by frozen section examination. The appendectomy was prophylactic, and the appendiceal disease was diagnosed as broad-based serrated adenoma, which is rare and belongs to precancerous lesions. Two rare pathological types occurred in the same patient at the same time, indicating the possibility of genetic changes. Therefore, NGS detection was carried out. No germline mutation was found. Only missense mutations of *PIK3CA* and *PTEN* were detected.

Among seven cases of mucinous tumors with mural nodules of anaplastic carcinoma, Mesbah Ardakani et al. [2] identified six cases with *KRAS* mutation. Therefore, it is inferred that the mural nodules of anaplastic carcinoma may originate from tumors with *KRAS* mutation. However, in 13 cases of mural nodules analyzed by Chapel et al. [7], only nine cases had *KRAS* missense mutations, and two had *PIK3CA* missense mutations. In Case 3, no *KRAS* mutation was found, while a *PIK3CA* missense mutation was identified. Therefore, *KRAS* mutation may not be associated with the formation of mural nodules. The *PTEN* mutation suggests that there signaling pathways other than the *KRAS* pathway are involved in tumorigenesis.

Recent studies suggest that loss of the SWI/SNF protein may play an important role in the de-differentiation of gynecological tumors. Mutations of *SMARCA4*, *SMARCB1*, *ARID1A* and *ARID1B* are

common in undifferentiated carcinoma, including undifferentiated components of de-differentiated carcinoma. It is reported that detecting the corresponding loss of protein expression can be regarded as a surrogate method for mutation of these genes. Chaudet et al. [9] found that nine of 25 mural nodules lacked expression of one or more SWI/SNF proteins, which was retained in all related mucinous tumors. Furthermore, the clinical outcomes of patients with SWI/SNF expression deficiency were often poor. In Case 3, immunohistochemical staining showed no loss of INI-1 expression in mucinous tumors and mural nodules, indicating that there was no *SMARCB1* mutation in this case (Fig. 2G).

Among the three cases reported here, blood NGS analysis was performed for only one case, and the other two cases were not tested for molecular markers. Moreover, NGS analysis of blood cannot be used to detect mucoepidermic and mural nodules.

In conclusion, young patients with SLMNs morphology, full pathological analysis should be undertaken to avoid the omission of malignant mural nodules. The expression of p53 in the mural nodules of anaplastic carcinoma was consistent with that in mucinous tumors. The serrated lesions of the appendix and ovarian mucinous tumor occurred simultaneously. No germline mutations were detected by NGS analysis, although there were missense mutations of *PIK3CA* and *PTEN*, indicating that this was a sporadic case.

Declarations

Ethics approval and consent to participate

All procedures performed on patient tumor samples in this study were in accordance with the ethical standards of the Institutional Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review Committee of the Shanxi Cancer Hospital and Institute (approval no.202122). Informed consent was obtained from parents and/or legal guardians for participants who are under age 18.

Consent for publication

Written informed consent was obtained from patients or parents and/or legal guardians for participants who are under age 18.

Availability of data and materials

Data and materials of this work are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Xiaojuan Wang and Peng Bu performed the histological and immunohistochemical(IHC) evaluation. Xiaojuan Wang and Yanfeng Xi were involved in literature review and drafted the manuscript; Pei Wang was involved in collecting clinical data. Chunyan Wang participated with the corresponding, reviewing, editing the drafted manuscript as per journal policy, and submission of the article. All authors read and approved the final manuscript.

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Competing interests

It is declared that all authors have no conflict of interest.

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Figures

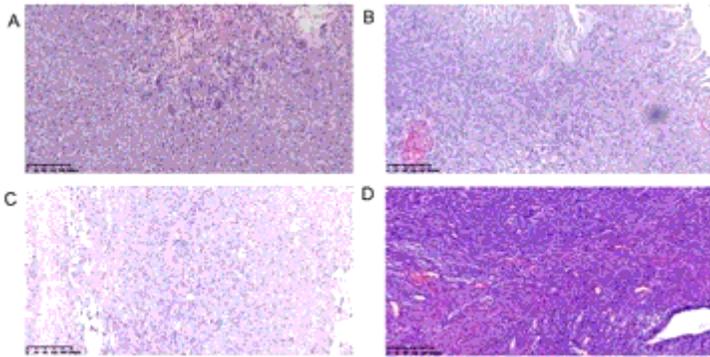


Figure 1

Microscopic morphology of mural nodules in three cases of anaplastic carcinoma (A) Sarcomatoid mural nodule in case 1(10×). (B) mural nodule of anaplastic carcinoma in case 1(10×). (C) mural nodule of anaplastic carcinoma in case 2(10×). (D) mural nodule of anaplastic carcinoma in case 3(10×).

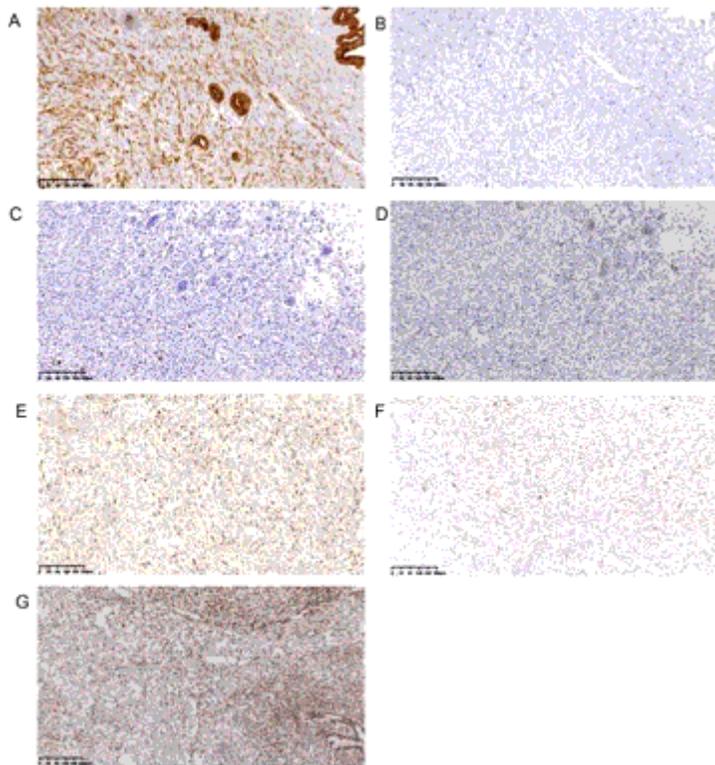


Figure 2

Immunohistochemical results (A)Expression of AE1/AE3 in mural nodules of anaplastic carcinoma in case 1(10×). (B)Expression of p53 in mural nodules of anaplastic carcinoma in case 1(10×). (C)Expression of AE1/AE3 in sarcomatoid mural nodule of case 1(10×). (D)Expression of p53 in sarcomatoid mural nodule of case 1(10×). (E)Expression of p53 in mural nodules of anaplastic carcinoma in case 2(10×). (F)Expression of p53 in mural nodules of anaplastic carcinoma in case 3(10×). (G) Expression of INI-1 in case 3(10×).

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