

# Clinicopathological Characteristics of Pseudomyxoma Peritonei Originated from Ovaries

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**Objective:** This study aims to demonstrate clinicopathological characteristics and immunohistopathological phenotypes of pseudomyxoma peritonei (PMP) originated from ovaries.

**Methods:** The primary origin of PMP was explored by reviewing H&E sections retrospectively and performing a series of immunohistochemical staining on CK7, CK20, CDX2, CEA, Villin, SATB2, CA125, ER, PR, and MUC.

**Results:** Among 310 PMP patients, a few originated from extra-appendix, whereas eight cases were of ovarian origin (2.6%), including three teratoma-associated ovarian mucinous tumors and five primary ovarian mucinous tumors with spontaneous or iatrogenic rupture, respectively. Most peritoneal metastases were acellular mucin or low-grade mucinous carcinoma peritonei (6/8, 75%), while the rest were high-grade mucinous carcinoma peritonei (2/8, 25%). Tumors were positive for CK20, CDX2, CEA, and Villin. SATB2 was specifically diffuse positive in teratoma-associated ovarian mucinous tumors, and negative in primary ovarian mucinous tumors. Differential expression of MUC was observed in these tumors.

**Conclusion:** PMP of ovarian origin is extremely rare. The precise diagnosis requires serial sections of the appendix or suspicious tissue to exclude appendiceal mucinous neoplasms, as well as comprehensive analysis of clinical features, surgical findings, histopathological characteristics, and immunohistochemistry on specific biomarkers.

**Keywords:** pseudomyxoma peritonei, PMP, ovary, mucinous tumor

## Introduction

Pseudomyxoma peritonei (PMP) is a unique and extremely rare clinical syndrome with an estimated incidence of 1–2 per million per year. It is characterized by extensive intraperitoneal mucinous effusion resulting from accumulation of gelatinous ascites or disseminated lesions of neoplastic mucinous epithelia. Etiologies of PMP primary tumors are originated most plausibly from mucinous neoplasms of the appendix. Occasionally, PMPs can stem from other abdominal and pelvic organs, in which the ovary is a rare origin.<sup>1,2</sup> Most PMPs originated from ovarian mucinous tumors were previously diagnosed clinically according to nonspecific findings from CT and MRI. In fact, these PMPs are metastases from appendiceal mucinous tumors to ovaries.<sup>3</sup> However, ovarian mucinous neoplasms are extremely rare sources of PMPs, which should be distinguished from benign causes of mucinous ascites and from appendiceal origin tumors. We performed the present study in an attempt to assess clinicopathological features of PMPs originated from ovaries, for a better understanding and management of these rare diseases.

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## Materials and Methods

### Case Selection

In this retrospective study, 310 PMP cases were included from 2013 to 2020 in Beijing Shijitan Hospital of Capital Medical University. After excluding those without definite primary tumor sources or a lack of preoperative clinicopathological information, only a few such as colorectal, ovary, urachus, and cervix uteri, were identified as primary extra-appendiceal sites. Notably, primary ovarian PMP (eight cases, 2.6%) was the most easily misdiagnosed. Imaging manifestations, clinicopathological findings, immunohistochemical staining, and a long-term follow-up were extracted from an electronic database of PMP patients who underwent cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The specific scope of CRS involved omentum, peritoneum, ligamentum teres hepatis, appendix, uterus and bilateral appendages, or rectum when appropriate. We had thoroughly inspected specimens and sampled all organs or tissues of each case according to gross sampling protocols. When diagnosed as extra-appendiceal sites, extensive sampling and serial multi-sites sections of the appendix were performed to exclude appendiceal mucinous neoplasms. This study was approved by the institutional review board and ethics committee of Beijing Shijitan Hospital and was conducted in accordance with requirements in the Declaration of Helsinki.

### Diagnostic Criteria

The hematoxylin and eosin (H&E) slides of tissue samples from surgical resection were retrieved to confirm histological diagnosis. Diagnosis was classified into four categories according to the 2016 Peritoneal Surface Oncology Group International (PSOGI) criteria:<sup>1</sup> acellular mucin (AC), low-grade mucinous carcinoma peritonei (LGMC), high-grade mucinous carcinoma peritonei (HGMC), and high-grade mucinous carcinoma peritonei with signet ring cells (HGMC-S).

Immunohistochemistry on CK7, CK20, CEA, CDX-2, SATB2, CA125, PAX8, WT-1, ER, PR, MUC1, MUC2, MUC5AC, MUC6, and Ki67 (OriGene) was performed on each slide using automated staining equipment (Biocare Medical). Appropriate positive control was established for each antibody according to manufacturer's instructions, and PBS was used as a blank control. The staining intensity was graded as negative, weak, intermediate, or strong. The staining distribution was classified as minimal, focal, or extensive (<10%, 11–50%, or >50%, respectively, of

a tumor section). All the slides were reviewed independently by two surgical pathologists, who were blinded to clinical and follow-up status.

## Results

### Clinical Features

The clinical manifestations of ovarian origin included abdominal mass, abdominal distention, change in body weight, ascites varying in amount, as well as abdominal or pelvic pain. Surgically, PMP was encountered as grossly visible mucin in the peritoneal cavity.

Most of the tumors exhibited unilateral, cystic solid masses. Patients were followed up for 2–109 months, no recurrence or metastasis was developed in two cases.

### Pathological Characteristics

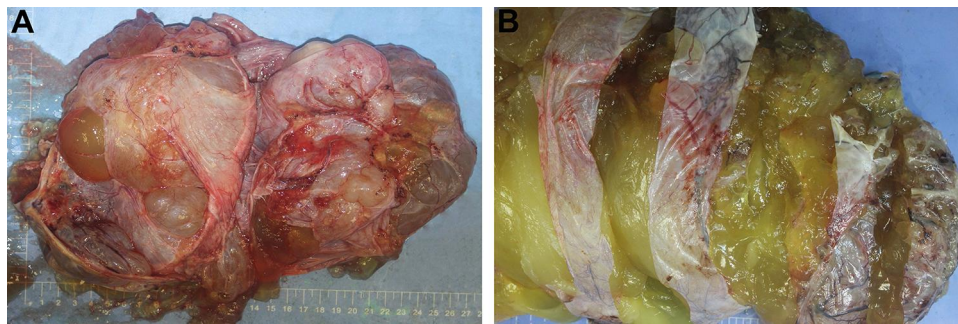
#### Ovary

Under macroscopy, ovaries contained multiloculated cystic solid masses of different sizes ( $4\times3\times3\text{ cm}^3$ – $35\times28\times11\text{ cm}^3$ ). The cysts had ruptured with jelly-like mucus/ascites overflowing around the abdominal or pelvic cavity. In general, the mucus of ovary origin was much thinner (Figure 1A) than that of appendix origin (Figure 1B). Grossly, none of the cases harbored components of teratoma (eg, skin, grease, or hair). Microscopically, five ovarian mucinous cystadenomas (62.5%) and three mucinous borderline tumors pushed forward or focally infiltrated tumor borders (37.5%, Figure 2A1) in the background, accompanied with partially pseudostratified nuclei at higher magnification. Three cases accompanied with mature ovarian teratomas composed of multiple germ components including skin appendages (Figure 2B1), respiratory epithelium, thyroid gland, and adipose tissue.

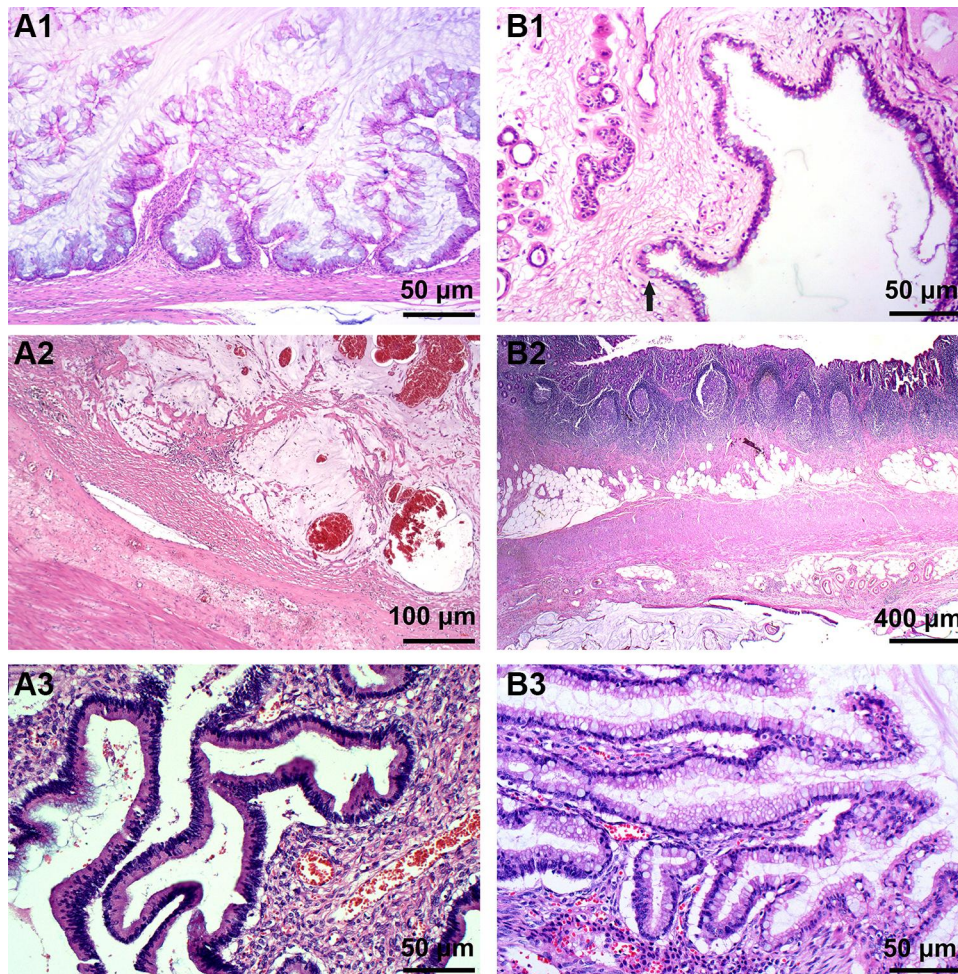
#### Peritoneum and Appendix

When ovarian tumors disseminated through rupture, gelatinous mucus and tumor cells overflowed around the abdominal or pelvic cavity. Jelly-like ascites varying in amount mainly existed in the peritoneum, as well as abdominal and pelvic cavities. The serosal surface of the appendix was normal or slightly rough with complete lumen structure. Microscopically, abundant mucinous pools exhibited in three cases (cases #1, 4, and 8), without any neoplastic epithelium (AC). In cases #3, 5, and 6, tumor components were arranged in a strip or small island shape, and tumor cells were columnar or flat with light heteromorphism (LGMC). In cases #2 and 7, tumor tissue was clustered, adenoid, and papillary, while tumor cells





**Figure 1** Clinical features of (A) ovarian PMPs vs (B) purely mucinous cystadenoma. Ovarian origin had much thinner mucus than appendiceal PMP that metastasizes to ovaries (which presented with significant gelatinous mucus).



**Figure 2** Histopathological features of ovarian PMPs. (A1) Ovarian mucinous borderline tumor with multiple-grade papillary structures (H&E, magnification  $\times 100$ ). (B1) Skin appendages with gastrointestinal-type mucinous gland (black arrow) (H&E, magnification  $\times 200$ ). (A2) Mucus in serous layer of appendix (H&E, magnification  $\times 50$ ). (B2) Low-grade neoplastic epithelium in serous layer of appendix (H&E, magnification  $\times 25$ ). (A3) Teratoma-associated mucinous neoplasm. Note obvious subepithelial cleft similar to that in low-grade appendiceal mucinous neoplasm involving ovary. (B3) Scanning magnification of primary ovarian gastrointestinal-type mucinous tumor, containing scattered goblet cells. (A3, B3) H&E, magnification  $\times 200$ .

were arranged in multiple layers, with obvious heteromorphism, without necrosis (HGMC). There was no lymph node involvement, angiolymphatic invasion, or perineural invasion.

Four layers of appendiceal structure were identified clearly, and no tumor presented in the mucosa. A small amount of acute/chronic inflammatory cell infiltration presented in the stroma, including a few mucoid (Figure 2A2)

**Table I** Main Clinicopathological Features of PMP Originating from Ovaries

Case ID	Age	Location (side)	Clinical Features	Type of Ovarian Tumor	Appendix	PMP Grade	Operation and Treatment	Operations (No.)	Follow-Up	Prognosis
1	75	left	Ovarian mass	Teratoma-associated mucinous borderline tumor	Chronic appendicitis with acellular mucus in serous layer	AC	CRS	1	25	No recurrence
2	45	right	Abdominal distention and pelvic mass	Teratoma-associated and mucinous borderline tumor with local infiltration	Acute simple appendicitis with low grade neoplasm in serous layer	HGMC	CRS+HIPEC	7	30	Survival with tumor
3	53	bilateral	Defecation difficulty	Teratoma-associated and mucinous cystadenoma	Chronic appendicitis with low grade neoplasm in serous layer	LGMC	CRS+HIPEC	3	29	Survival with tumor
4	73	left	Abdominal distention and pelvic mass	Mucinous cystadenoma and preoperative spontaneous rupture	Chronic appendicitis	AC	CRS	2	83	No recurrence
5	56	right	Abdominal mass	Mucinous cystadenoma with rupture during multiple operation	Chronic appendicitis	LGMC	CRS+HIPEC	4	109	Survival with tumor
6	56	left	Abdominal distention and mass	Mucinous cystadenoma with rupture during multiple operation	Chronic appendicitis with low grade neoplasm in serous layer	LGMC	CRS+HIPEC	3	52	Survival with tumor
7	32	left	Abdominal distention	Mucinous borderline tumor with rupture during multiple operation (including laparoscopic operation)	Chronic appendicitis	HGMC	CRS+HIPEC	4	33	Survival with tumor

(Continued)

**Table 1** (Continued).

Case ID	Age	Location (side)	Clinical Features	Type of Ovarian Tumor	Appendix	PMP Grade	Operation and Treatment	Operations (No.)	Follow-Up	Prognosis
8	72	left	Abdominal discomfort	Mucinous cystadenoma and preoperative spontaneous rupture	Chronic appendicitis with acellular mucus in serous layer	AC	CRS+HIPEC	1	2	Survival with tumor

**Abbreviations:** AC, acellular mucin; LGMC, low-grade mucinous carcinoma peritonei; HGMC, high-grade mucinous carcinoma peritonei.

or low-grade/high-grade mucinous epithelium tumors (Figure 2B2) in the serosa layer.

Histological characteristics could be divided into two groups, one was teratoma-associated mucinous tumor. Scalloped glands (comprising of irregular and elongated glands dissected into ovarian stroma, which were related to pseudomyxoma ovarii<sup>4</sup>) were lined by “tall cells” with a low nuclear to cytoplasmic ratio (Figure 2A3). These glands separated the mucinous epithelium from stroma, thus forming a subepithelial cleft. Another one was a purely primary gastrointestinal-type ovarian tumor with conventional mucinous glands containing goblet cells (Figure 2B3), which were surrounded by ovarian-type stroma. Focal papillae and/or subepithelial stromal clefts could be observed occasionally. Scalloped glands or pale histiocyte aggregates (mucin granulomas) were not obvious. In ovarian mucinous borderline tumors, atypical glands displayed complex intraluminal papillary projections; however, their external contours were relatively rounded and circumscribed (Table 1).

## Immunohistochemical Staining Results

CK7 was negative in three cases, including one case originated from teratoma-associated mucinous tumor (Figure 3A1), whereas it was positive in one case (case #8, Figure 3B1). CK20 was diffuse (Figure 3A2) or partial positive (Figure 3B2) in all cases. CDX2 was positive with different intensity (Figure 3A3 and B3). SATB2 (nuclear matrix binding region binding protein 2) was positive in all three cases originated from teratoma-associated mucinous tumors (Figure 3A4), whereas negative in cases originated from purely ovarian mucinous tumors (Figure 3B4), also focal positive in ovarian mucinous tumors. CEA and Villin were strongly positive in all cases. Pax8, WT-1, ER, and PR were negative. The Ki67 proliferation index was 10–60%. CA125

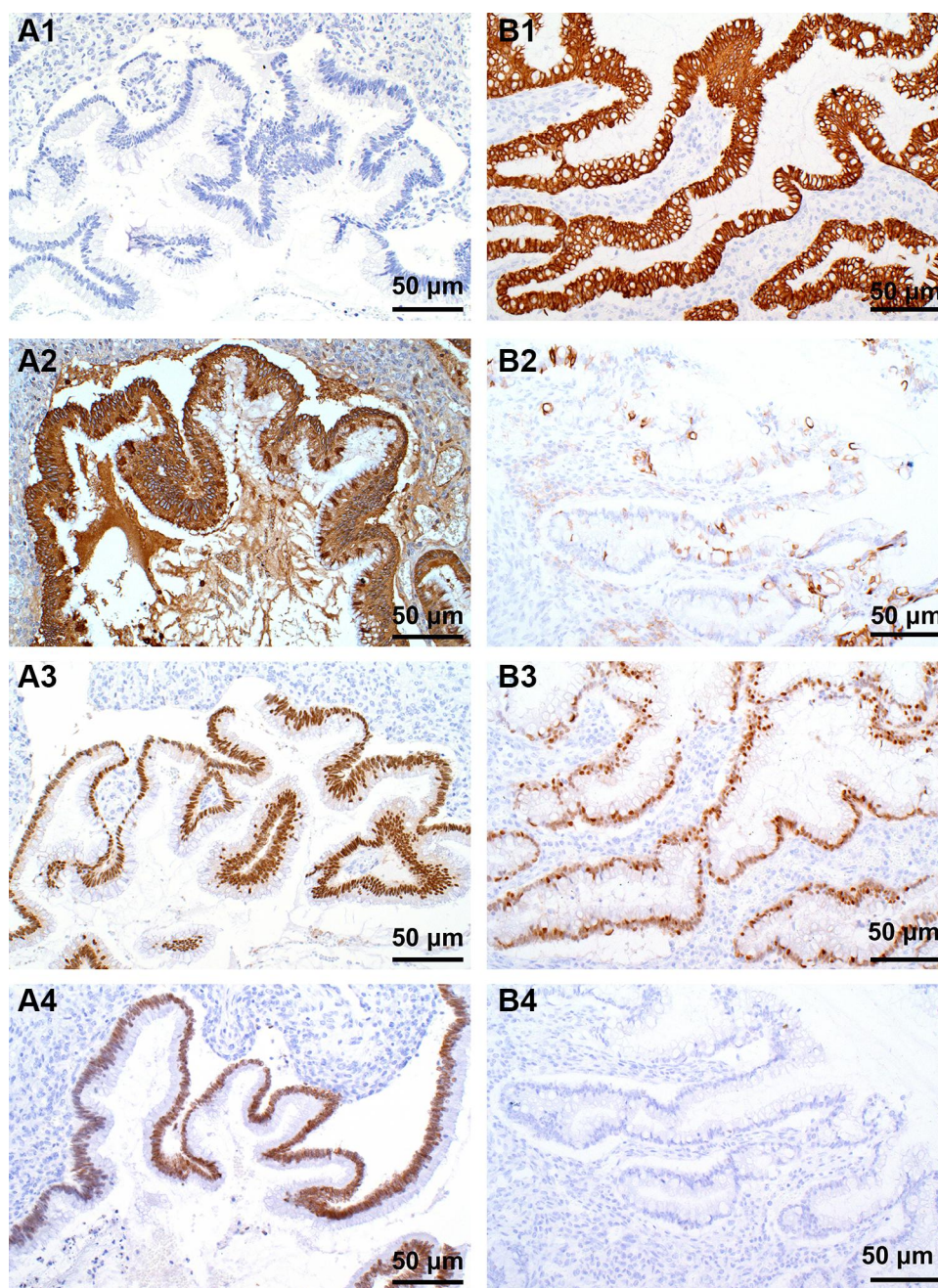
was focal positive in two cases. Most MUC family members were positive (MUC1: 6/8, MUC2: 7/8; MUC5AC: 8/8; MUC6: focal 2/8, Figure 4A1–B4) (Table 2).

## Discussion

PMP is a rare clinical disease, typically characterized by gelatinous myxoperitoneal effusion, progressive abdominal distention, and obstruction. Under macroscopy, a large amount of jelly-like ascites were widely distributed in the abdominal/pelvic cavity. There has been a debate about the origin of the primary tumor. PMPs were considered to arise from many organs, such as the appendix, ovary, fallopian tube, pancreas, urachal tube, colon, and rectum.<sup>5–8</sup> Recently, based on clinicopathology, immunohistochemistry, and molecular pathology, researchers have confirmed that the vast majority of PMPs stem from ruptured mucinous tumors of the appendix.<sup>9</sup> Usually, low-grade mucinous carcinoma peritonei is related to low-grade appendix mucinous neoplasm (LAMN), whereas high-grade mucinous carcinoma peritonei related to appendiceal mucinous adenocarcinoma. Pathologically, transition from normal epithelium of the appendix to LAMN/HAMN/mucinous adenocarcinoma could provide direct histological evidence for PMP originating from the appendix.<sup>10–12</sup>

Metastatic ovarian mucinous tumors are complex and vary by exhibiting pathological morphology of multi-directional differentiation, from benign, borderline, to malignant evolution. In female patients with PMP, the appendix and ovary could be involved simultaneously or successively. Because of no exploration or previous operation of the appendix, PMP cases were often misdiagnosed and mis-treated as primary ovarian neoplasms. Based on extensive specimen collection of appendices in combination with comprehensive evaluation of medical history, most cases





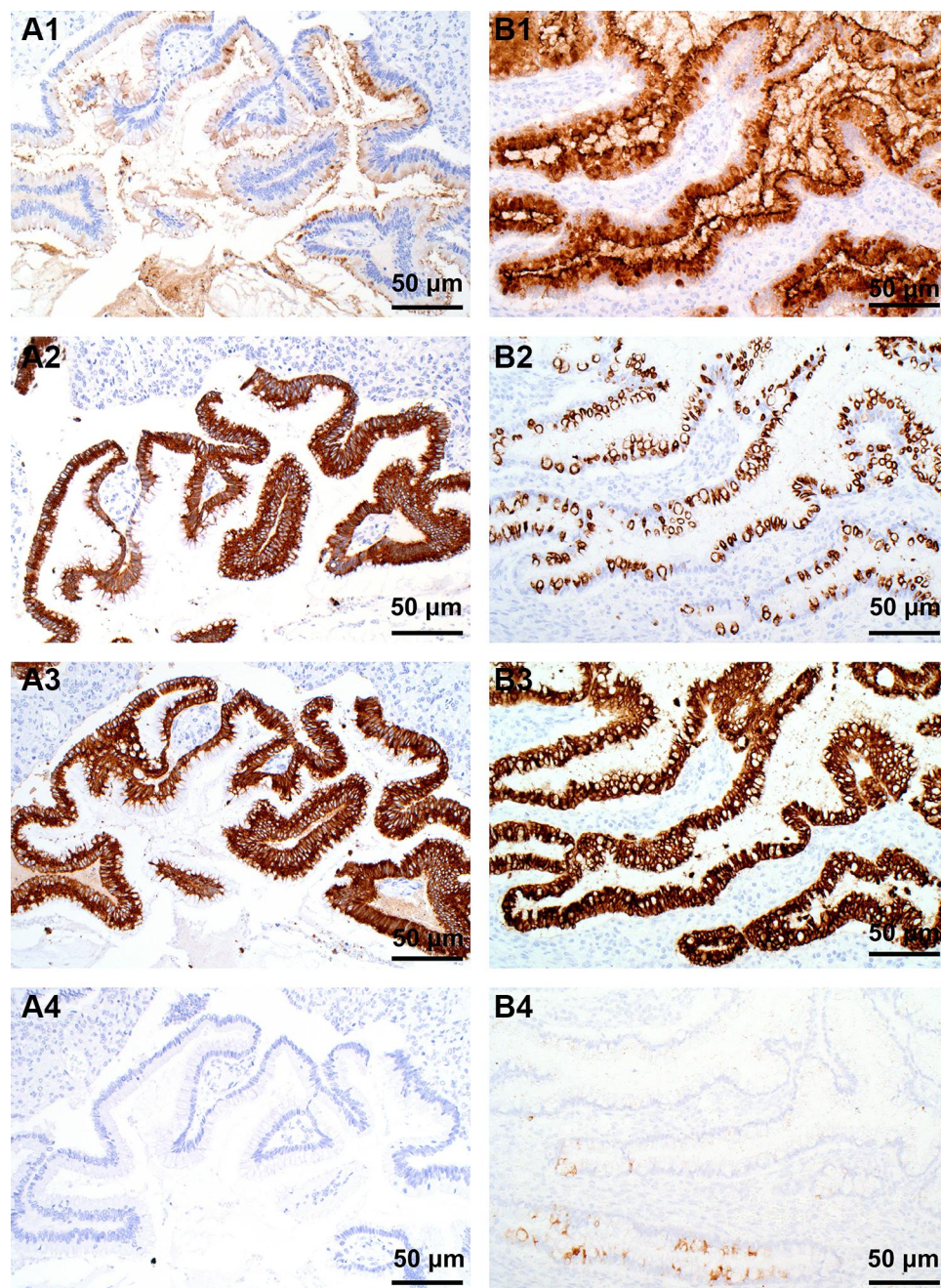
**Figure 3** Immunohistochemical staining in PMPs originated from ovaries. Teratoma-associated mucinous tumors were (A1) Negative for CK7, (A2) Strongly positive for CK20, (A3) Positive for CDX2, (A4) Strongly positive for SATB2. PMPs originated from purely ovarian mucinous tumor were (B1) Strongly positive for CK7, (B2) Scattered positive of goblet cell for CK20, (B3) Weakly positive for CDX2, (B4) Negative for SATB2. (A1-B4) EnVision staining  $\times 200$ .

originated from the appendix.<sup>13</sup> NCCN has pointed out that primary malignant ovarian mucinous tumors were very rare. It is highly recommended to make comprehensive evaluation of the upper or lower digestive tract to exclude metastasis. Conventional appendectomy is necessary for ovarian mucinous tumors (even if the appendix was grossly normal). However, only a few studies focused on clinicopathological features of PMPs originating from ovaries. Some PMPs

originate from teratoma or result from preoperative spontaneous rupture.<sup>14–18</sup>

Histological morphology,<sup>4</sup> such as tall mucin-rich columnar epithelial cells, irregular budding glands, and contracted space around glands, suggests appendiceal origin. In this study, three PMP cases were teratoma-associated ovarian mucinous tumors. These tumors had distinctive histological features involving hypermucinous epithelial





**Figure 4** Immunohistochemical staining in PMPs originated from ovaries. Teratoma-associated mucinous tumors were (A1) Weakly positive for MUC1, (A2) Diffusely strong positive for MUC2, (A3) Diffusely positive for MUC5AC, (A4) Negative for MUC6. Primary ovarian mucinous tumor was (B1) Weakly positive for MUC1, (B2) Scattered positive of goblet cell for MUC2, (B3) Diffusely positive for MUC5AC, (B4) Focal positive for MUC6. (A1-B4) EnVision staining  $\times 200$ .

cells, scalloped glands, and subepithelial stromal clefts, very similar to classical appendiceal origin. The association of mucinous cystadenomas with teratoma might represent a malignant transformation in the gastrointestinal epithelium of germ-cell origin.

The rest of the PMPs were purely primary ovarian mucinous tumors with preoperative spontaneous rupture or undergoing intraoperative rupture and implantation,

which led to mucus dissemination in abdominal and pelvic cavities. Occasionally, rupture of cysts could be obvious under a microscope. Scalloped glands, subepithelial stromal clefts, and histiocyte aggregates were not prominent, however, reactive ovarian-type stroma was more significant, while stromal invasion was absent.

In this study, the majority of PMPs of ovarian origin were acellular mucin or low-grade mucinous carcinoma

Table 2 Immunohistochemical Markers for Ovarian Teratoma-Associated Mucinous Tumor and Primary Ovarian Mucinous Tumor

Case ID	Tumor Site	CK7	CK20	CDX2	SATB2	CEA	Villin	CA125	PAX8	WT-1	ER	PR	MUC1	MUC2	MUC5AC	MUC6	Ki-67
1	Ovary	+	+	+	+	+	+	.	.	.	.	.	+	+	+	.	20%
2	Peritoneum	+	+	+	+	+	+	.	.	.	.	.	+	+	+	.	60%
3	Peritoneum	.	+	+	+	+	+	Focal+	.	.	.	.	+	+	+	.	60%
4	Ovary	.	+	+	.	+	+	.	.	.	.	.	.	+	+	.	10%
5	Peritoneum	.	+	+	.	+	+	.	.	.	.	.	+	+	+	.	40%
6	Peritoneum	+	+	+	Focal+	+	+	.	.	.	.	.	+	+	+	.	20%
7	Peritoneum	+	Partial+	Partial+	.	+	+	.	.	.	.	.	+	.	+	Focal+	40%
8	Ovary	+	Partial+	+	.	+	+	Focal+	.	.	.	.	+	+	+	Focal+	80%

peritonei (75%). The prognosis of ovarian origin was better than the appendix or colorectum (85.7 vs 72.8 or 34.0 months,  $P=0.002$ ) during long-term postoperative follow-up according to a previous study in a large patient population of PMPs.<sup>19</sup> Surgeons should pay more attention to avoid potential rupture of iatrogenic myxomatous tumor and intraoperative colloidal mucus dissemination in abdominal and pelvic cavities. Rupture of ovarian mucinous tumors can occur without any abdominal symptoms or only with painless abdominal distention.

Immunohistochemical markers CA125, ER, PR, Pax8, and WT1 were expressed to different degrees in primary epithelial ovarian tumors. Most of them failed to distinguish a specific origin of PMP.<sup>20</sup> CEA or Villin had low specificity and limited value in identifying original tumor. We used serial makers (CK7, CK20, CDX2, and SATB2) to make a differential diagnosis. SATB2 is a highly specific marker for colorectal and appendiceal tumors. It has a highly specific nuclear expression pattern in malignancies located in the lower gastrointestinal tract.<sup>21</sup> SATB2 was negative in primary ovarian mucinous neoplasms (except for teratomas), which could aid in distinguishing metastatic ovarian mucinous neoplasms from primary ovarian mucinous lesions.<sup>22–25</sup> In our study, one PMP case originating from purely ovarian mucinous tumor was focal positive for SATB2, probably due to limited material acquisition (insufficient sampling) or teratomatous components.

To sum up, to clarify accurate origin of complicated PMP remains challenging. For PMP patients indicated by imaging, abdominal puncture or laparotomy, appendectomy, and exploration of bilateral ovaries should be performed routinely. Extensive multiple lesions of ovarian tumors should be sectioned and all suspicious appendiceal tissues should be sampled for definite diagnosis. Simultaneously, previous medical history and histopathological sections, intraoperative conditions and histomorphology should be comprehensively analyzed. Scalloped glands, subepithelial clefts, cellular stroma, and histiocyte aggregates in combination with immunohistochemical markers (eg, CK7, CK20, CDX2, and SATB2) may be useful parameters to help distinguish the origin of PMP and to evaluate biological behavior of PMP from different origins (except teratoma-associated tumors).

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. The study protocol was approved



by the Medical Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (Beijing, China).

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## Disclosure

The authors report no conflicts of interest in this work.

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