



Article

## Pseudomyxoma peritonei — a heterogenous disease

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### Abstract

*Objective:* To evaluate the origin of pseudomyxoma peritonei (PMP) in Chinese women. *Methods:* The clinicopathologic features of 15 cases of PMP were reviewed. Immunostaining using antibodies for CK7 and CK20 was performed in the ovarian, appendiceal and peritoneal lesions of these cases. *Results:* Appendiceal pathology was documented in five cases, including four mucinous cystadenoma and one simple mucocele. Eight ovarian tumors were found, including seven mucinous cystadenocarcinomas of low malignant potential and one mucinous cystadenoma. Synchronous ovarian and appendiceal lesions were discovered in three cases. One patient had adenocarcinoma of the pancreas. The origin of mucin production was not known in four cases with metastatic adenocarcinoma found in two of them. Immunoreactivity for CK20 was demonstrated in the tissues derived from the peritoneum, ovary, appendix and pancreas while only 23% (3 out of 13 women) of the peritoneal lesions and 33% (2 out of 6 women) of the ovarian tumors were immunoreactive for CK7. *Conclusions:* PMP is a heterogeneous lesion, which may develop from mucinous metaplasia of the peritoneum or from appendiceal, or ovarian lesions. Careful examination of the ovary and appendix with performance of appendectomy is advised in every case of PMP. Immunohistochemical examination of the peritoneal, ovarian or appendiceal lesions using antibodies, in particular that for CK7 would help in defining the origin of mucin production. © 1998 International Federation of Gynecology and Obstetrics

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## 1. Introduction

Pseudomyxoma peritonei (PMP) is an uncommon disease first described in 1884 by Werth in association with a mucinous tumor of the ovary [1]. It is characterized by the accumulation of abundant mucinous material within the peritoneal cavity. Benign or malignant epithelial cells may or may not be found in the mucinous deposit. PMP has been found to be associated with benign and malignant neoplasms of several organs. While the appendix and the ovary are the organs most commonly involved [2–11], other organs including the Fallopian tubes, pancreas, and the intestinal tract have also been reported to give rise to PMP [12–14]. In some cases, the primary origin of PMP may be difficult to ascertain.

Cytokeratin 7 (CK7) is a simple epithelial keratin reported to be positive in primary ovarian adenocarcinoma but negative in gastrointestinal adenocarcinoma [15–17] while cytokeratin 20 (CK20) is expressed predominantly in the epithelial cells of the gastrointestinal tract [17–19].

In this study, we have reviewed clinicopathological features and performed immunohistochemical studies using antibodies for CK7 and CK20 in 15 cases of PMP diagnosed in women in an attempt to clarify the origin of mucin production in PMP.

## 2. Materials and methods

### 2.1. Selection of cases and clinicopathological review

Fifteen cases of pseudomyxoma peritonei diagnosed in the period from 1975 to 1996 were retrieved from the pathology files of Queen Mary Hospital, the University of Hong Kong (14 cases) and People's Hospital, Beijing Medical University (one case). All of the patients were women and most of them have been operated by gynecological surgeons. The clinical and pathology records as well as all the available cytology and histology slides were reviewed with emphasis on the age, sites of mucin deposit, macroscopic and microscopic findings and the survival data of these patients.

### 2.2. Immunohistochemistry

Formalin-fixed paraffin-embedded tissue blocks of the primary lesions including ovarian, appendiceal and pancreatic tumors, as well as peritoneal lesions of the above mentioned cases were retrieved. Eight cases of primary ovarian mucinous cystadenocarcinoma and two cases of colonic adenocarcinoma were included as control. Thick sections (5  $\mu\text{m}$ ) were cut and mounted on 2% aminopropyltriethoxysilane-coated glass slides. The sections were de-waxed in xylene and rehydrated through graded concentrations of alcohol. Endogenous peroxidase was blocked using 3% hydrogen peroxidase in methanol. Microwave pretreatment for antigen retrieval similar to previously described reports [20] was then carried out. The sections were immersed in 10 mmol/l (pH = 6) sodium citrate buffer in a thermoresistant plastic box and processed in a microwave oven at 95°C for 20 min. The sections were then cooled in sodium citrate buffer and then transferred to Tris-buffered saline (TBS) before immunostaining. Immunohistochemistry was performed using the strept-avidin-biotin complex (S-ABC) immunoperoxidase method (Dako, Glostrup, Denmark). The monoclonal mouse anti-human antibodies for cytokeratin 7 and cytokeratin 20 (Dako, Glostrup, Denmark) were applied at 1:50 dilution and incubation was performed at 4°C overnight. Biotinylated rabbit anti-mouse antibody was used as the linker molecule and diaminobenzidine-hydrogen peroxide was used as chromogen. A light Mayer's hematoxylin counterstain was used. Sections were dehydrated in alcohol, cleared in xylene and mounted. In the negative control section, Tris-buffer was used instead of the specific antibodies.

## 3. Results

### 3.1. Clinicopathological features

The clinicopathologic findings are summarized in Table 1. These 15 cases of pseudomyxoma peritonei were found in women with ages ranging from 36 to 88 years (average 60 years). All patients

Table 1  
Clinicopathologic and immunohistochemical features of 15 cases of PMP

Case	Appendix				Ovary				Other				Follow up
	Gross	Microscopy	CK7	CK20	Gross	Microscopy	CK7	CK20	Gross	Microscopy	CK7	CK20	
3	Gelatinous mass	Mucinous cystadenoma	-	+	Bilateral multicystic masses	Mucinous LMP	+	+	Mucinous omental mass	Benign mucinous epithelium	++	++	Died after 2 years
13	Roundish nodule	Mucinous cystadenoma	-	+	Left multicystic mass	Mucinous LMP	-	+	Mucinous omental mass	Mucin only; no epithelium	No epithelium		Alive after 1 year
7	Cystic mass	Mucinous cystadenoma	ND	ND	Left multicystic mass	Mucinous LMP	ND	ND	Mucinous omental mass	Benign mucinous epithelium	++	++	FF
11	Implant nodules	Not resected	ND	ND	Right multicystic mass	Mucinous LMP	+	++	Mucinous omental mass	Benign mucinous epithelium	+	++	Alive after 1 year
8	Normal	Normal	-	++	Left multicystic mass	Mucinous LMP	-	++	Mucinous omental mass	Mucin only; no epithelium	No epithelium		Alive after 7 years
9	Normal	Not resected	ND	ND	Normal	Not resected	ND	ND	Gelatinous omental nodules Nodular pancreatic mass	Metastatic (signet-ring cell) carcinoma Poorly differentiated adenocarcinoma	- -	++ ++	Died after 2 years
14	Normal	Normal	-	+	Bilateral multicystic masses	Mucinous LMP	-	++	Mucinous omental mass	Benign mucinous epithelium	-	++	Alive after 1 year
2	Normal	Not resected	ND	ND	Left multicystic mass	Mucinous cystadenoma	-	++	Mucinous omental mass	Benign mucinous epithelium	-	++	Died after 1 year

Table 1 (Continued)

Case	Appendix				Ovary				Other				Follow up
	Gross	Microscopy	CK7	CK20	Gross	Microscopy	CK7	CK20	Gross	Microscopy	CK7	CK20	
5	Ruptured cystic mass	Mucocoele with atrophic mucosa	–	++	Unknown	Unknown	ND	ND	Mucinous peritoneal mass	Benign mucinous epithelium	–	++	FF
12	Ruptured cystic mass	Mucinous cystadenoma with rupture	–	+	Unknown	Unknown	ND	ND	Mucous deposit in peritoneum	Benign mucinous epithelium	–	++	FF
4	Unknown	Unknown	ND	ND	Bilateral multiloculated cysts	Mucinous LMP	ND	ND	Mucinous peritoneal mass	Benign mucinous epithelium	–	+	Died after 1 year
1	Unknown	Unknown	ND	ND	Unknown	Unknown	ND	ND	Mucinous omental mass	Benign mucinous epithelium	–	++	FF
15	Unknown	Unknown	ND	ND	Unknown	Unknown	ND	ND	Mucinous omental mass	Benign mucinous epithelium	–	+	Died after 6 months
6	Unknown	Unknown	ND	ND	Unknown	Unknown	ND	ND	Gelatinous peritoneal nodule	Metastatic adenocarcinoma	–	++	FF
10	Unknown	Unknown	ND	ND	Unknown	Unknown	ND	ND	Gelatinous omental nodules	Metastatic adenocarcinoma	–	++	FF

Abbreviations: Mucinous LMP, mucinous cystadenocarcinoma of low malignant potential; FF, defaulted follow-up.

presented with abdominal pain, distention and ascites and underwent laparotomy.

The macroscopic state of the appendix was described in 10 patients (Cases 2, 3, 5, 7, 8, 9, 11–14). Four appendices appeared normal at laparotomy (Case No. 2, 8, 9, 14). The other six (3, 5, 7, 11–13) appeared either as cystic mass distended with mucin or had mucinous deposit at the serosa. Two were complicated by rupture (Cases 5, 12). Seven appendices have been resected, including five that were grossly abnormal (Cases 3, 5, 7, 12, 13). No significant pathological lesions could be found during examination of the two macroscopically normal appendices (Cases 8, 14). Among the grossly abnormal appendices, four were diagnosed to be mucinous cystadenoma (Cases 3, 7, 12, 13) while one was found to be a mucocele (Case 5) where the mucosa was partially atrophic. There is no evidence of malignancy in all the appendices examined.

Ovarian tumors were found in eight cases (Cases 2–4, 7, 8, 11, 13, 14). Four of them were found at the left side (Cases 2, 7, 8, 13), one at the right side (Case 11) while the other three cases were bilateral (Cases 3, 4, 14). Histologically, seven were diagnosed as mucinous cystadenocarcinoma of low malignant potential (LMP) while the remaining one was a mucinous cystadenoma. All of these tumors show intestinal differentiation of variable degrees. Synchronous ovarian and appendiceal lesions were found in three patients (Cases 3, 7, 13). Ovarian mucinous LMP and appendiceal mucinous cystadenoma were diagnosed in all these three cases.

Mucinous adenocarcinoma arising from the pancreas was found in one patient (Case 9). In this case both ovaries and appendix were normal. In four other patients, the origin of mucin production was unknown (Cases 1, 6, 10, 15). Knowledge of the state of the ovaries or appendix was not available since such information could not be retrieved from the archival records.

When the mucinous deposits from the peritoneal cavity were examined, benign mucinous epithelium was identified in 10 cases. Cytological features diagnostic of adenocarcinoma was noticed in three cases (Cases 6, 9, 10) with signet ring cell found in Case 9.

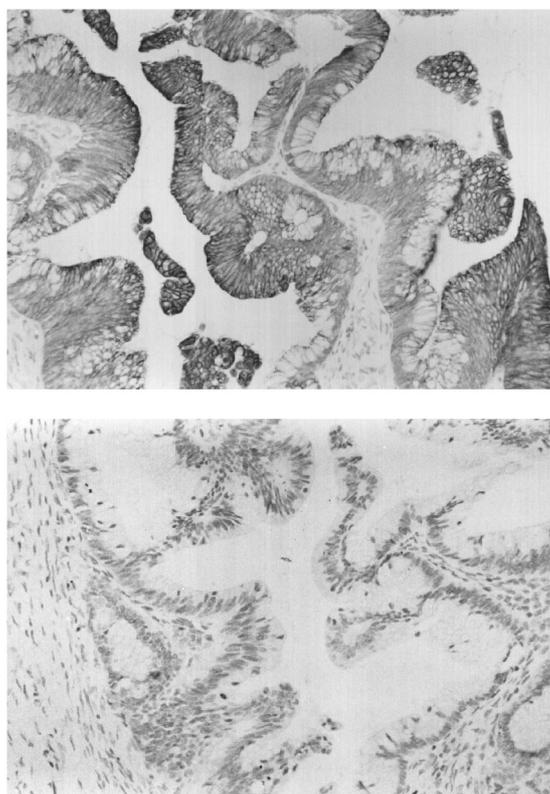


Fig. 1. Ovarian mucinous cystadenocarcinoma of low malignant potential (Case 14). The tumor was immunoreactive for CK20 (A) but not CK7 (B).

Survival data were obtained for nine patients. Five patients died of the disease 6 months to 2 years after operation (Cases 2, 4, 11, 13–15). One patient was still alive 7 years after diagnosis (Case 8). The remaining three patients (Cases 11, 13, 14) have only been followed up for 1 year. They were alive at that time but defaulted afterwards.

#### 4. Immunohistochemistry

Immunohistochemical staining patterns for CK7 and CK20 are summarized in Table 1. Immunoreactivity for CK20 was demonstrated in all the tissues derived from the peritoneum, ovary, appendix and pancreas (Fig. 1). On the other hand, only 23% (3 out of 13 women) of the peritoneal lesions (Cases 3, 7, 11) and 33% (2 out of 6 women) of the ovarian tumors were positive for

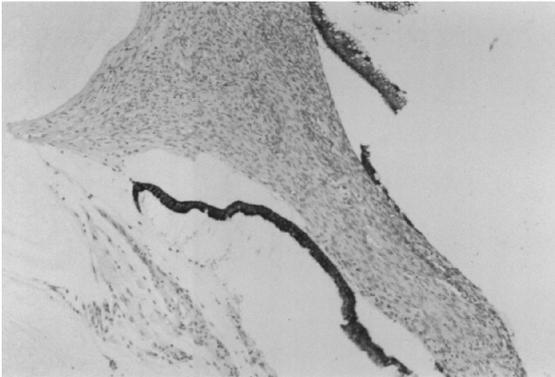
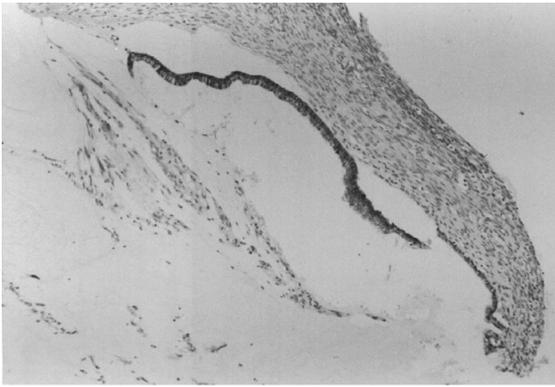


Fig. 2. Ovarian mucinous cystadenocarcinoma of low malignant potential (Case 3). The tumor was immunoreactive for both CK20 (A) and CK7 (B).

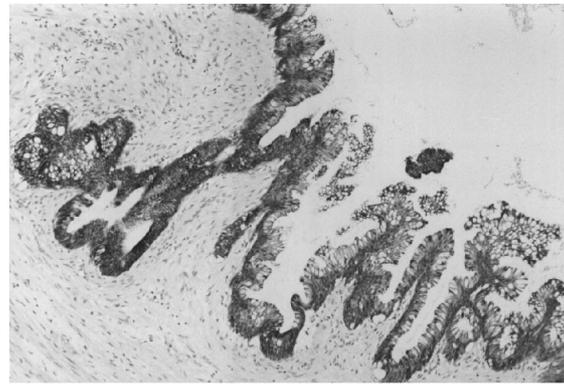


Fig. 3. Mucinous cystadenoma of appendix (Case 3). The tumor was immunoreactive for CK20 (A) but not CK7 (B).

CK7 (Cases 3, 11). None of the lesions from appendix and pancreas were immunoreactive for CK7.

Paraffin blocks were only available in two out of the three cases with synchronous ovarian and appendiceal tumors (Cases 3, 13). In Case 3 (Figs. 2–4), both the ovarian and the peritoneal lesions were immunoreactive for CK7. While the epithelium of the appendiceal mucinous cystadenoma was negative for CK7 as expected, the benign epithelium associated with the mucinous deposit found at the appendiceal serosa was immunoreactive for CK7. Thus, this case appears to represent a case of synchronous primary tumors in which peritoneal implants (CK7+) may be of ovarian origin with a coincidental appendiceal cystadenoma (CK7–). In Case 13, both the ovarian or appendiceal lesions were negative for CK7 and no

epithelium was identified in the peritoneal mucin for immunostaining.

In Case 7, the benign epithelium found in the peritoneal mucin was immunoreactive for both CK7 and CK20. Unfortunately, paraffin blocks were not available from the appendiceal or ovarian lesions of Case 7 to draw further conclusions.

Among the control sections, seven of the eight cases with primary ovarian mucinous adenocarcinoma showed strongly positive reaction for CK7 and six of them were also positive for CK20. The two cases of colon adenocarcinoma were negative for CK7 but positive for CK20.

## 5. Discussion

In spite of the numerous series of PMP reported, there is still considerable controversy

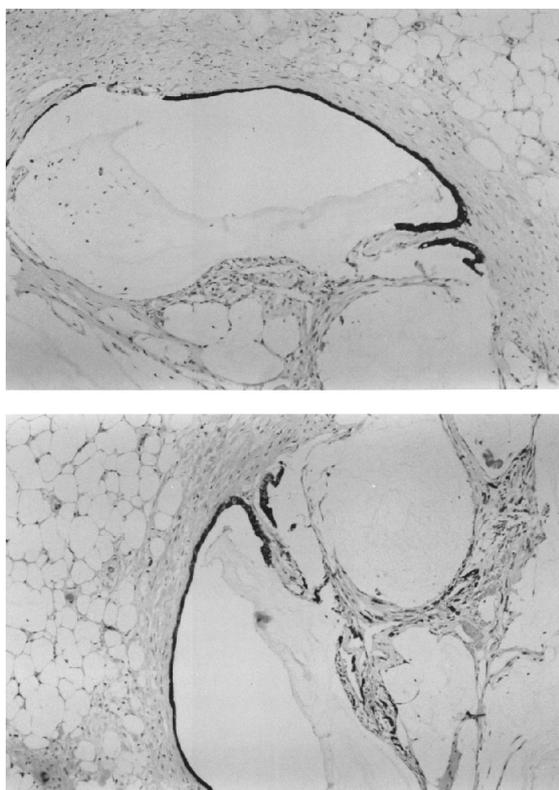


Fig. 4. Mucinous epithelium in the peritoneal deposit at the appendiceal serosa (Case 3). The epithelium was immunoreactive for both CK20 (A) and CK7 (B).

about this disease. The origin of the disease is one of the issues that trigger considerable argument. There has been much discussion concerning whether PMP originates from implants of a primary mucinous tumor or as part of a multifocal neoplastic process. The determination of the origin of PMP is particularly complicated in women with coexisting appendiceal and ovarian mucinous tumors.

Some investigators believe that the appendix is the primary origin in most cases of PMP [3,6,8,9,11] while the peritoneal and ovarian lesions are metastatic lesions, despite the fact that metastatic appendiceal carcinoma to the ovaries is rare [21]. This hypothesis is based on several observations. First, a high incidence of appendiceal lesions has been found in patients with PMP. Adenomatous or even carcinomatous

changes have often been detected in these appendices. Moreover, ovarian tumors detected in patients with PMP and coexisting appendiceal lesions are often bilateral or right-sided [5,6] and are thus considered to be secondary. Furthermore, immunohistochemical studies using antibodies for CK7, CK18, CK20, CEA and HAM56 on synchronous appendiceal and ovarian mucinous tumors associated with PMP also favor the interpretation that the ovarian tumors and the peritoneal lesions are probably metastasis from the appendiceal tumor [8,9]. Cuatrecasas et al. [22] in their study on comparative analysis of c-Ki-ras mutations [22], also demonstrated the clonal nature of these synchronous ovarian and appendiceal tumors associated with PMP, suggesting that these tumors probably arise from the same origin and are not independent tumors.

The relationship of ovarian tumor and PMP is also unclear. Although primary ovarian mucinous LMP is not uncommon in women, the incidence of PMP complicating these ovarian tumors is low. In the review by Kaern et al. [23] on 370 cases of ovarian mucinous LMP, PMP was only found in 30 cases (8%) [23]. It has been noted that those ovarian tumors found with PMP frequently show intestinal differentiation [25] and it has thus been suggested that ovarian tumors with PMP and those without PMP are separate pathologic entities [24]. The incidence of PMP is also 3–4 times more common in women than in men ([26], personal observation). These findings support the hypothesis that PMP may represent metaplasia of the peritoneum into mucinous epithelium [27] and the ovarian and appendiceal lesions may occur as a neoplastic field change [28]. This is comparable to the well-accepted theory about the histogenesis of primary serous tumors arising from the female peritoneum [29,30].

In our study, the appendices which have been examined were either normal or showed only benign epithelial changes such as mucinous cystadenoma or simple mucocoele. Two of the appendiceal masses, including one mucocoele and one mucinous cystadenoma had ruptured and were considered to be the origin of PMP. Thus, our series are different from previous studies on ap-

pendiceal lesions associated with PMP in that none of our cases has been associated with carcinoma of the appendix. On the other hand, three of our eight ovarian tumors associated with PMP were bilateral; four were located at the left side while one was detected at the right side. Histologically, seven of the eight ovarian tumors were mucinous LMP while the remaining one was a mucinous cystadenoma. Three of the appendiceal mucinous cystadenomas were found to coexist with ovarian mucinous borderline tumors. The histology of the appendiceal and ovarian lesions were thus different from that reported in the literature.

CK7 and CK20 have been proposed to be useful tools in distinguishing ovarian from colonic carcinomas [15–18]. We found CK20 to be unhelpful since it is universally positive in lesions of intestinal type differentiation even if arising in the ovary. On the other hand, CK7 is selectively positive in ovarian tumors only. This observation was also made by Tenti [31] and confirmed in our control blocks.

In our study, all six ovarian tumors with available blocks showed a positive reaction for CK20 and all of them showed some degree of intestinal differentiation. On the other hand, only two ovarian tumors were immunoreactive for CK7 (Cases 3, 11). The associated peritoneal lesions in these two CK7 positive ovarian tumors were also immunoreactive for CK7 suggesting a similar origin. The peritoneal lesion of Case 7 also showed a positive reaction for CK7. Unfortunately, no paraffin block was available from the ovarian or appendiceal lesions for immunostaining. Among the three cases with synchronous ovarian and appendiceal tumors (Cases 3, 7, 13), paraffin blocks are only available in two cases. Case 3 appears to represent a case of synchronous primary tumors since both the ovarian and the peritoneal lesions, including those found at the appendiceal serosa, were immunoreactive for CK7. The epithelium of the appendiceal mucinous cystadenoma, on the other hand, was negative for CK7. The peritoneal epithelial deposit (CK7+) may thus be of ovarian origin with a coincidental appendiceal cystadenoma (CK7-). In case 13, CK7 immunoreactivity could not be demonstrated

in the ovarian, appendiceal or peritoneal lesions supporting the possibility of the appendiceal lesion being the primary site of mucin production.

After integration of the clinicopathological features and immunohistochemical findings, we have attempted to deduce the origin of PMP in our 15 cases based on the following criteria. An appendiceal origin is favored if: (1) the appendix was the only abnormal organ detected; and/or (2) the ovarian tumors were bilateral or right sided. On the other hand, the PMP is unlikely to be of appendiceal origin if: (1) the appendix showed no histological abnormality; and/or (2) the peritoneal and ovarian lesions were immunoreactive for CK7. In these cases, the PMP may arise as secondary implants from the ovary or as a result of peritoneal metaplasia. Using these criteria, we decided that two cases were probably of appendiceal origin (Cases 5, 12), four cases were unlikely to arise from the appendix but were possibly of ovarian or peritoneal origin (Cases 3, 7, 8, 11). One case definitely arises from the pancreas (Case 9). The origin of PMP could not be assessed in four cases (Cases 1, 6, 10, 15), two of them were associated with metastatic adenocarcinoma (Cases 6, 10). Definite conclusions could not be drawn in the remaining four cases (Cases 2, 4, 13, 14) because of inadequate data in the records.

To conclude, we believe that PMP is a complicated lesion. While a fraction may arise secondary to an appendiceal lesion, some of them may arise from the ovary. It could also derive from metaplasia and hyperplasia of Mullerian epithelium that cover the peritoneum besides constituting the surface epithelium of the ovary. This may explain the concordant immunophenotype in some cases. In order to be able to more clearly delineate the origin of PMP, the ovary and the appendix should be carefully examined during laparotomy of PMP. If possible, biopsy of the ovary and appendectomy, even when the appendix appears grossly normal should always be performed. Immunostaining of peritoneal, ovarian and appendiceal lesions using antibody for CK7 should also be performed to help establish the origin of PMP.

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