# Multicystic mesothelioma has malignant potential: its grounds and mechanisms of peritoneal metastasis

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## Abstract

From 2009 to 2016, 9 female patients with multicystic peritoneal mesothelioma (MCPM) underwent 11 cytoreductive surgeries (CRS). Mean age at diagnosis was 50.6 (range, 43-71). Mean peritoneal cancer index was 8.9 (range, 2~33).

Most frequent peritoneal sector involved was pelvic peritoneum in 7 patients, and greater omentum was involved in 6 patients. Eight and 1 patients had complete CRS and incomplete CRS, respectively. Except 1 patient, 8 patients had multiple cysts on different peritoneal sectors, and diffuse involvement on peritoneal surface was found in 2 patients No patients had lymph node metastasis or extraperitoneal spread. However, 3 patients showed pushing invasion to small bowel mesentery, colon, umbilicus and stomach. Median- follow-up was 46 months (range 4-120). At the time of the present analysis, all patients were alive. One patient recurred in peritoneal cavity 47 month after complete cytoreduction.

Peritoneal free-floating cysts (PFFC) were found in 8 of 9 (88.9%) patients. Sizes of PFFC ranged from 1 mm to 2 cm in diameter and the inner surfaces were covered with mesothelial-like cells. MIB-1 labeling rates of PFFC ranged from 0.1% to 2.0%. These results indicate that PFCC may attach on the orifice of subperitoneal lymphatic vessels, and may become metastatic.

The present study strongly suggests that MCPM has a potentially malignant behavior. This category of disease is composed of 2 types: diffuse type and localized type with borderline malignant potential. PFFC have an important role in the formation of peritoneal metastasis.

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## Introduction

Multicyctic peritoneal mesothelioma (MCPM), considered as extremely rare tumor is a multilocular cystic tumor usually arising from the pelvic peritoneum, particularly the cul-de-sac, uterus, and rectum. Approximately 200 cases of MCPM have been reported from 1979 to 2015.[1-3] However, the etiology remains unknown. Although the disease has shown an indolent clinical behavior after cytoreductive surgery (CRS) in most cases, early recurrence after complete resection,[2,3] transformation to diffuse peritoneal mesothelioma,[1,4-6] and even death due to compression of bowel have been described.[1-3]

For the present study, results of CRS for MCPM and pathological findings are reported. Additionally, the mechanisms of metastasis from primary are discussed.

## Materials and Methods

All the patients were treated in accordance with protocol approved by ethical committee of Kishiwada Tokushukai Hospital and Kusatsu General Hospital. Informed consent was obtained from and signed by each patient.

Standardized clinical data on consecutive patients were entered into a database. The data consisted of patient characteristics (age, sex, tumor marker levels), clinical history (exposure to asbestos, previous operation) clinical diagnosis, presenting symptoms, intraoperative findings (peritoneal cancer index, primary site, location of tumor), operation methods (completeness of cytoreduction, combined resection, scalloping), and pathologic findings (haematoxylin/eosin and immunohistochemical staining).

### Operative findings and treatment

After midline incision, all of peritoneal sectors was thoroughly observed and investigated with palpation. Peritoneal cancer index (PCI) was recorded. PCI is a semi-quantitative score that combines lesion size of 0 to 3 with disease distribution in 13 abdomino-pelvic sectors, and PCI score ranges from 0 to 39.[7]

Cytoreductive surgery was performed using aqua dissection methods.[6] The goal of CRS was to remove all the macroscopically detected tumors. If the cysts showed scalloping or adhesion to visceral organs, local excision or multivisceral resections were performed.

The completeness of cytoreduction (CCR score) was determined after CRS, as follows: CCR-0 = no visible residual tumor, CCR-1 = residual disease ≤2.5 mm, CCR-2 = residual disease >2.5 mm and ≤25 mm ; CCR-3 = residual tumor ≥25 mm.[8]

After CRS, 6 patients were treated with hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C (MMC) at a dose of 12.5 mg/m$^2$ and cisplatin (CDDP) at 50 mg/m$^2$ in 4L of saline at an intraperitoneal temperature between 42.5 and 43.5 centigrade. Before and after CRS, extensive intraoperative peritoneal lavage (EIPL) using physiological saline is performed. To perform EIPL, 1 L of saline is administered into the peritoneal cavity, and the saline is completely aspirated by a suction tube equipped with loosely woven filter. The procedure is repeated 10 times.

Follow-up consisted of physical examination and serum tumor marker level determination every 6 months. Patients also underwent magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CECT) every 6 months. Recurrence was diagnosed, when MRI and CECT showed an abnormality typical of a cystic tumor recurrence. No patient was lost at follow-up.

### Statistics

Overall and progression-free survival was calculated from the day of CRS to the last follow-up date.

## Results

### Patient characteristics

From November 1996 to 2016, 9 patients underwent 11 CRS procedures (Table 1). All patients were females and no patients had a documented history of asbestos exposure. Mean age at diagnosis was 50.6 (range, 43-71). Three and 2 patients complained of abdominal fullness (Case 1, 4, 6) and abdominal pain (Case 3, 5), respectively. Three patients had received operation for other disease (Case 1, 2, 7).

Preoperative diagnoses were pseumyxoma peritonei, appendiceal tumor and ovarian tumor in 7 (Case 1, 2, 5, 6, 7, 8, 9), 1 (Case 3), and 1 (Case 4), respectively. On MRI scan of case 1, multiple cysts occupied in peritoneal cavity, and scalloping to small bowel was found (Figure 1A). From these findings, she was diagnosed with pseudomyxoma peritonei. Serum tumor marker levels were elevated in 3 patients, and elevated serum CEA (Case 1), CA19-9 (Case 2) and CA125 (Case 2, 8) were found in 1, 1, and 2 patients.

The lesions were described as multiple, translucent membraneous cysts that were grouped together to form a confluent mass or studded the surface of the peritoneum in a discontinuous fashion (Figure 2). The cysts varied in size from a few millimeters to larger than 10 cm in diameter and were filled with fluid, which varied in color from clear (Figure 3A) to blood-tinged fluid (Figure 3B and C). No excrescence or solid area was identified. Primary sites were

**Table 1. Patients' characteristics, primary sites, tumor location, CCR score, scalloping, operation procedures, hyperthermic intraperitoneal chemotherapy, recurrence, peritoneal-free floating cysts, and prognosis.**

| No. | Age | Gender | Primary site | Tumor laction (sector No.) | PCI Score | CCR | Scalloping |
|---|---|---|---|---|---|---|---|
| 1 | 71 | Female | Greater omentum | 0, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 | 33 | 3 | Yes (small bowel) |
| 2 | 54 | Female | Pelvic peritoneum | 6, 12 | 2 | 0 | No |
| 3 | 43 | Female | Right paracolic gutter | 0, 6, 7, 8 | 6 | 0 | No |
| 4 | 50 | Female | Sigmoid colon | 6 | 3 | 0 | No |
| 5 | 55 | Female | Caecum | 0, 6, 7 | 6 | 0 | No |
| 6 | 57 | Female | Unknown | 0, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12 | 18 | 0 | Yes (umbilicus) |
| 7 | 49 | Female | Greater omentum | 0,6 | 4 | 0 | No |
| 8 | 46 | Female | Uterus | 6 | 2 | 0 | No |
| 9 | 52 | Female | Lesser omentum | 0, 2, 6, 7 | 10 | 0 | Yes (stomach) |

| Organs and peritoneum removed | HIPEC | Recurrence | PFFC | Prognosis |
|---|---|---|---|---|
| Biopsy | Not done | Non curative | po | 8Y 8M alive with disease |
| Hys. BSO, omentectomy, sect. 6 | Done | No | po | 2Y 3M alive |
| rHC, right SO, omentectomy | Done | No | po | 1Y 5M alive |
| rHC, Hys, BSO | Done | No | po | 5Y 9M alive |
| Omentectomy, sect. 6 | Done | No | po | 10M alive |
| rHC, LAR, Hys, BSO, sect. 0, 4, 5, 6, 7, 8, 10, 12 | Not done | Recurrence | po | 3Y 11M recurrence, 10Y 3M alive with disease |
| rHC, omentectomy | Not done | No | po | 3Y 3M alive |
| Hys. BSO, sect. 0, 6 | Done | No | ne | 7 M alive |
| BSO, omentectomy, sect. 0, 2, 6, 7 | Done | No | po | 5M alive |

PCI, peritoneal cancer index; CCR; completeness of cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; PFFC, peritoneal free floating cysts; po, positive; Hys., hysterectomy; BSO, bilateral salpingo-oophorectomy; rHC, right hemicilectomy; LAR, low anterior resection; ne, negative.

2 from greater omentum, and 1 each from uterus, caecum, ascending colon, sigmoid colon, right paracolic gutter, and pelvic peritoneum. Primary site was not identified in 1 patient (Case 6) (Table 1), because multiple cysts were diffusely distributed in the peritoneal cavity. In Case 5, large cyst and multiple small cysts were found on caecum, and the lesion was considered as primary site (Figure 3A). After meticulous observation, one blood-tinged cyst of 1 cm in diameter was found on greater omentum (Figure 3B and C).

Interestingly, peritoneal free-floating cysts (PFFC) were found in 8 of 9 (88.9%) patients (Figure 4). Sizes of peritoneal free-floating cysts ranged from 1 mm to 2 cm in diameter, and were filled with clear fluid.

Mean PCI was 8.9 (range, 2-33). Tumor location is shown in Table 1. Peritoneal sectors of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 were involved in 6, 1, 2, 1, 2, 2, 9, 5, 3, 2, 2, 2, and 1 patients, respectively. Most frequent sector involved was pelvic peritoneum, and greater omentum was involved in 6 patients (Table 1).

Operation procedures are presented in Table 1. Hysterectomy with bilateral salpingo-oophorectomy was the most commonly performed procedure, being carried out in 6 patients, Omentectomy was performed in 6 patients, and colon resection was performed in 6 patients. Resection of sector 6 (pelvic peritoneum) was performed in 4 patients, and sector 5, 6, 7, 8, 10, and 12 were removed in 1 patient (Case 6). Colostomy was made in 1 patient (Case 6). No operation death and no grade 3 or 4 morbidity occurred.

Seven patients had CCR-0 CRS and 1 patient had CCR-3. No patients had lymph node metastasis or extraperitoneal spread. However, 2 patients showed pushing invasion (scalloping) to small bowel and colon (Case 1, Figure 1B and C), subcutaneous tissue of umbilicus (Case 6, Figure 5), and stomach (Case 9).

## Survival and treatment failure

Median- follow-up was 49 months (range 7-123). At the time of the present analysis, all patients were alive. One patient (Case 6) recurred in peritoneal cavity 47 month after complete cytoreduction, but she was alive with disease 123 months after CRS. Overall 5-year survival rate was 100%.

## Pathological features

The tumors consisted of cysts of various sizes, and the inner surface was lined by a single layer of flattened to cuboidal mesothelial-like cells with stromal edema, lymphocyte infiltration and fibroblastic proliferation. In Case 2 and 6, pushing invasion of cysts into subcutaneous tissue at umbilicus (Figure 5), muscle

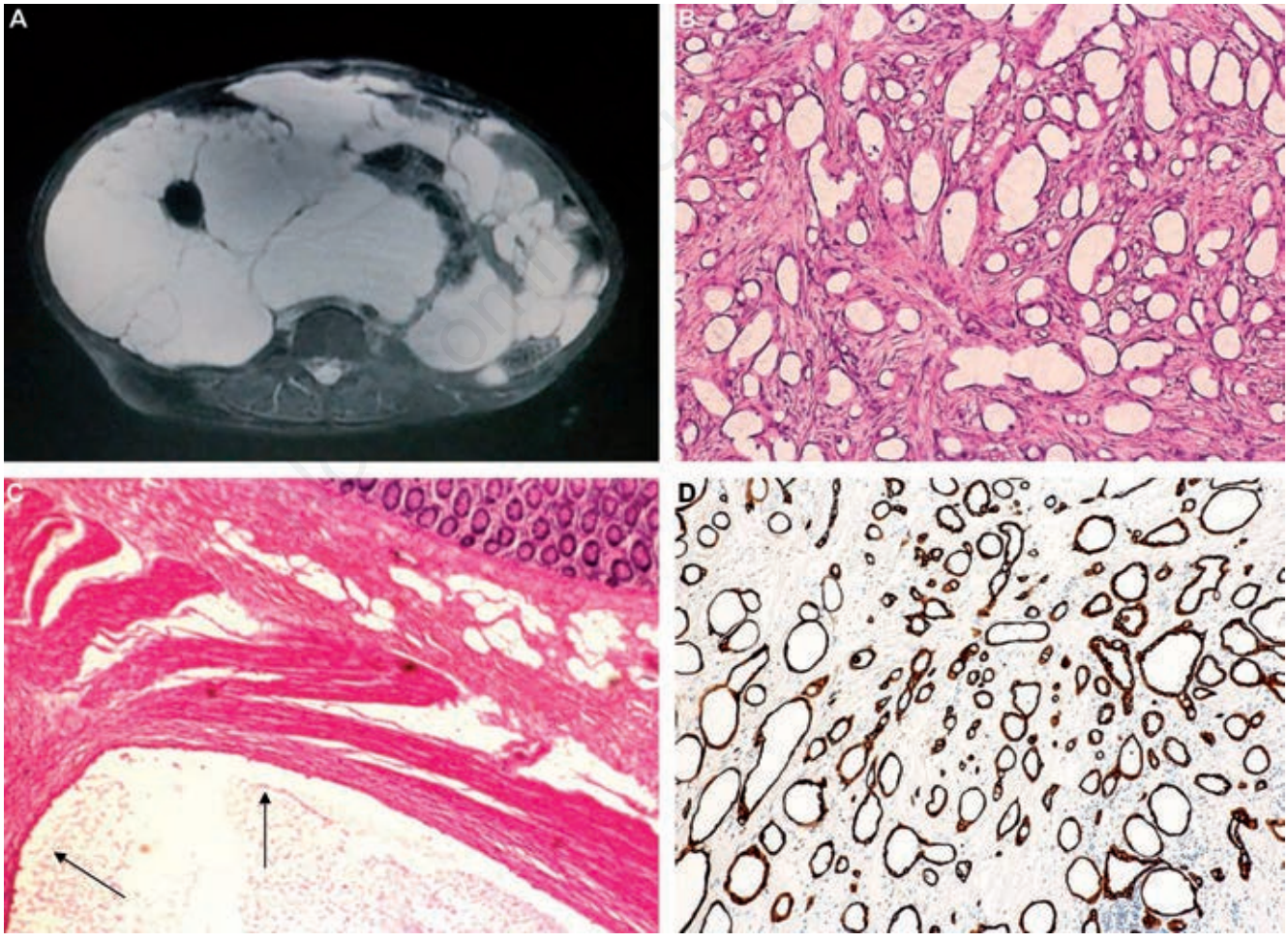


**Figure 1. Case 1: A) T2-weighted coronal MRI image shows multiloculated cysts occupied in peritoneal cavity. Scalloping of small bowel and its mesentery was found; B) Many cysts infiltrating into small bowel mesentery; C) Pushing invasion of cyst into colonic muscle; D) Positive epidermal growth factor immunoreactivity on mesothelial-like cells lined on the inner surface of cysts in small bowel mesentery.**

layer of transverse colon and small bowel mesentery were found (Figure 1B and C). Biological markers were investigated using immunohistochemistry (Table 2). Cytokeratin 7, mesothelin, and HEBM-1 were positive in all patients, and calretinin was expressed in 7 of 9 patients. In contrast, CD31 and CD34 were negative in the lining cells in all patients. One patient showed positive immunoreactivity against D2-40. Positive reactions were found in the cytoplasm of mesothelial-like cells. Immunohistological staining revealed that EGFR were strongly expressed on the cell membranes of mesothelial-like cells of cysts (Figure 6B).

Ki67 expression was detected in nucleus, and Ki67 labeling indices ranged from 0.1% to 2.0% (Figure 1D). Mitosis was rarely found in mesothelial-like cells.

The inner layer of PFFC (Figure 6A) was lined by cuboidal of flat mesothelial-like cells.

## Discussion

MCPM occurs most frequently in young to middle-aged women (mean age, 37 years), and men (mean age, 47 years) represent 16% of cases 2, 4). It has many alternative names, including peritoneal inclusion cyst, multilocular inclusion cyst, and benign multicystic mesothelioma. It grows along the serosa as multiple, translucent, fluid-filled cysts.[1-3] Because of the association of previous pelvic operation in young women, and no relation with asbestos exposure, this disease may develop by inflammatory reaction.[1] Additionally, it has shown an indolent biological behavior in the majority of patients, and the postoperative survival has been good. Accordingly, MCPM is considered a nonneoplastic, reactive mesothelial proliferation, and was initially considered as a benign disease with better prognosis.

However, a recent multi-institutional study showed that 50% of patients have recurrence 1-27 years after the initial diagnosis.[2,6]

**Figure 2. Case 8: Resected multicystic mesothelioma showing multiple fluid-filled cysts on uterus. Cysts connected with fine stalks from uterine surface.**

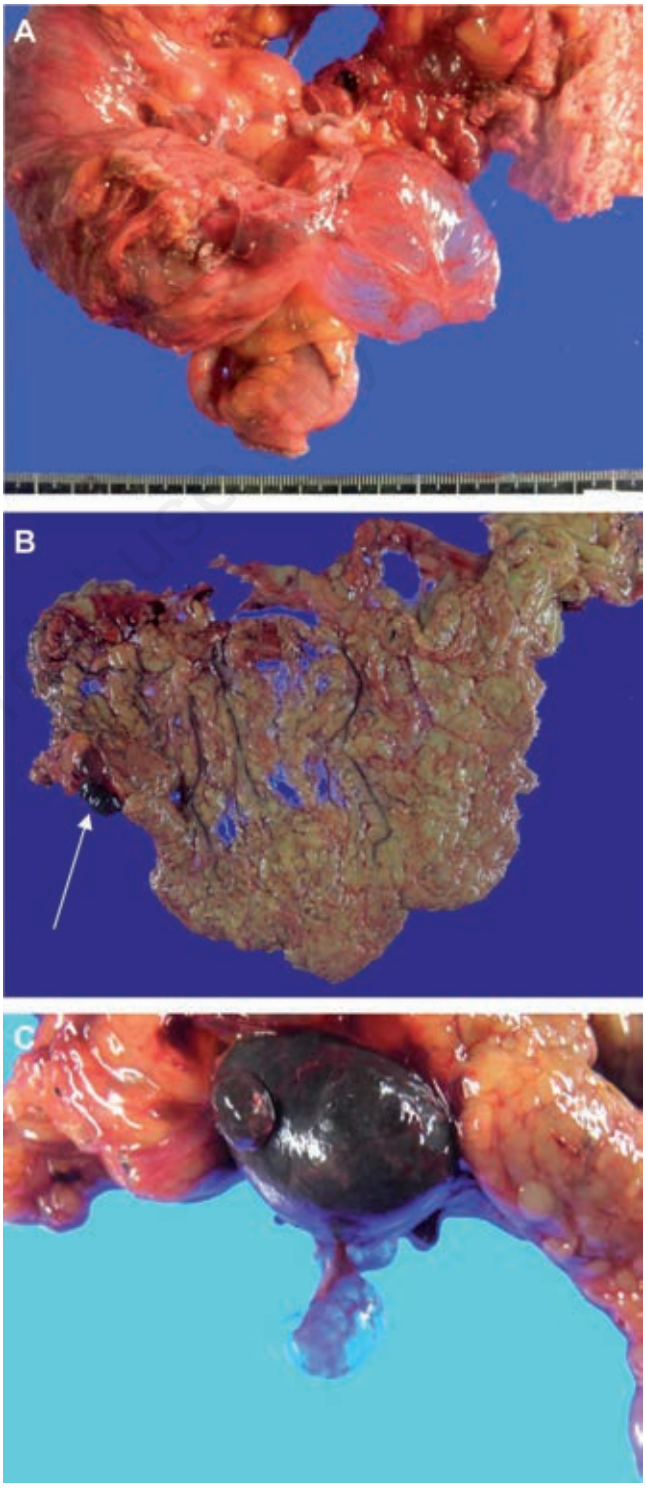


**Figure 3. Case 5: A) Resected multicystic mesothelioma showing fluid-filled cysts on caecum; B) and C) Cyst with blood-tinged fluid was also found on greater omentum.**

Some authors considered it to be a mesothelial neoplasm because it may recur locally and in rare cases may show malignant transformation.[4,9]

In the present study, Case 1 had diffuse involvement of peritoneal surface by the cystic tumors and pushing invasion into mesentery. Case 6 recurred 3 years and 11 months after complete cytoreduction, and histologic findings showed invasion of small cysts into subcutaneous tissue of umbilicus. These 2 patients had higher malignant potential than the other 6 patients. Accordingly, MCPM may be composed of two subtypes: *i.e.* diffuse type (Case 1, 6) and localized type with borderline malignant potential (Case 2, 3, 4, 5, 7, 8, 9).

Ki-67 antigen is a nuclear protein expressed during all phases of cell cycles except G0 phase. Accordingly, MIB-1 index is a sensitive marker of proliferation and tumor aggressiveness. MIB-1 index of diffuse peritoneal mesothelioma is reported to range from 0.6% to 10%.[10-12] MIB-1 index higher than cutoff level in diffuse peritoneal mesothelioma correlates with poor outcome. In contrast, MIB-1 indices were low in the present 9 cases, These results may indicate that MCPM has malignant potential with low proliferative activity.

A very interesting finding in the present study was PFFC, which was found in 8 of 9 patients. PFFC may detach from pri-

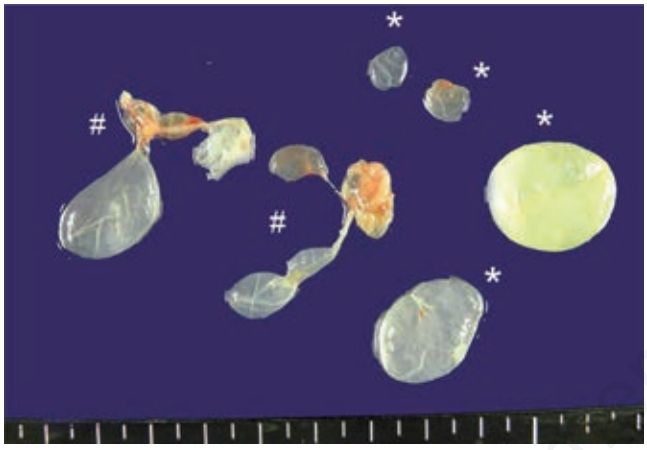


**Figure 4. Case 3: Peritoneal free-floating cysts (*), and cysts connects with thin stalk on peritoneal surface (#).**

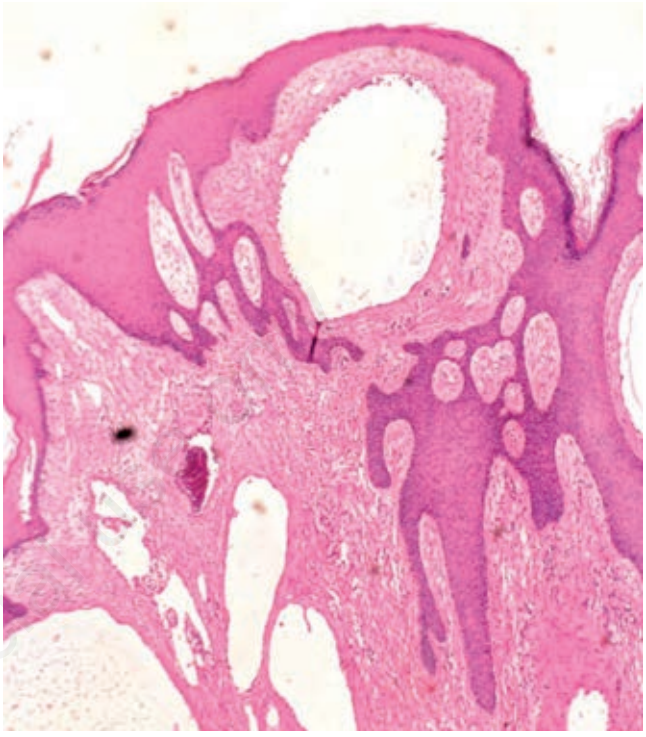

**Figure 5. Case 6: Pushing invasion of cysts into subepidermal tissue in umbilicus.**

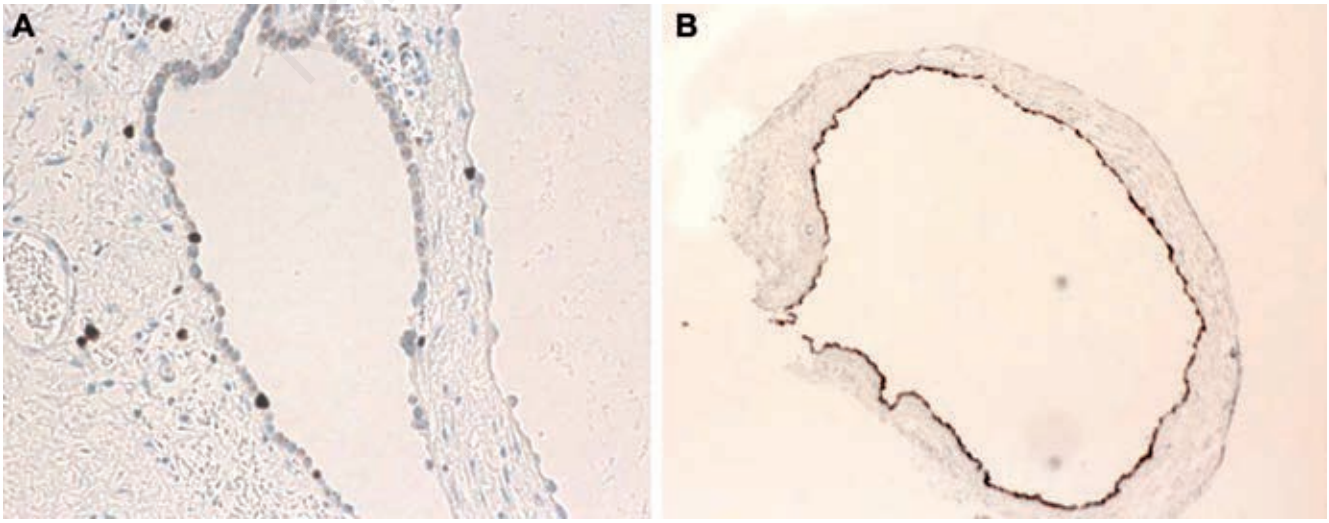


**Figure 6. A) Case 4: Anti-Ki-67 antibody immunoreaction of mesothelial-like cells lined on the inner surface of cysts; B) Positive immunoreaction to anti-mesothelin antibody was detected on mesothelial-like cells lined on the inner surface of peritoneal free-floating cyst.**

**Table 2. Immunohistologic findings.**

| Cases | D2-40 | Calretinin | CK7 | HBME1 | Mesothelin | MIB-1 index | CD34 | CD31 | EGFR |
|---|---|---|---|---|---|---|---|---|---|
| 1 | ne | po | po | po | po | 1% | ne | ne | po |
| 2 | ne | po | po | po | po | 2% | ne | ne | po |
| 3 | ne | po | po | po | po | 1% | ne | ne | NT |
| 4 | ne | po | po | po | po | 2% | ne | ne | po |
| 5 | po | ne | po | po | po | 2% | ne | ne | po |
| 6 | ne | ne | po | po | po | 0.10% | ne | ne | NT |
| 7 | ne | po | po | po | po | 0.10% | ne | ne | po |
| 8 | ne | po | po | po | po | 1% | ne | ne | po |
| 9 | ne | po | po | po | po | 1% | ne | ne | po |
| Total | 1/9 (11.1%) | 7/9 (78%) | 9/9 (100%) | 9/9 (100%) | 9/9 (100%) | 0.1~2% | 0/9 (0%) | 0/9 (0%) | 7/7 (100%) |

po, positive; ne, negative; NT, not tested.

mary lesion when thin stalk connecting to peritoneal surface break. As a result, cysts migrate in the peritoneal cavity. They migrate on the peritoneal surface, and are held on the cul-de-sac of pelvis by gravity. PFFCs attach on the lymphatic orifice opening on the peritoneal surface or on the milky spots in greater omentum, because lymphatic orifice and milky spots have a role in the absorption of peritoneal fluid.

Inner layers of PFCC were covered with mesothelial-like cells, and these cells have proliferative activity as shown in Ki-67 immunostaining. PFCCs that attach on lymphatic orifice proliferate by the supply of nutrients and oxygen from the glomerular arterial blood capillaries in the omental milky spots,[13] and metastasis is established.

Accordingly, HIPEC and aggressive peritoneal lavage using saline may be effective to remove peritoneal free-floating cysts, resulting in reducing recurrence after CRS.[14] However, use of anticancer drugs during HIPEC may not be necessary.

## Conclusions

MCPM has a potentially malignant behavior, and has an invasive potential into neighboring organs. This category of disease is composed of 2 types: diffuse type and localized type with borderline malignant potential. PFFC have an important role in the formation of peritoneal metastasis.

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