Autopsy Case Reports

Article / Clinical Case Report

Benign multicystic peritoneal mesothelioma: literature review and update

Momal Tara Chand[a], Jacob Edens[b], Tayson Lin[c], Ian Anderson[b], Richard Berri[d]

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ABSTRACT

Benign multicystic peritoneal mesothelioma (BMPM) is a rare peritoneal tumor diagnosed predominantly in pre-menopausal women. Associated risk factors include endometriosis and pelvic inflammatory disease in women, and prior abdominal surgery in both genders. To date, the pathogenesis of this disease remains controversial with possible etiologies, including a neoplastic versus a reactive process. Given the risk factors, some authors believe that this disease is secondary to a reactive process. However, because some studies describe cases where there is no prior surgical history or inflammatory milieu present, and because of this entity's predilection for recurrence, some authors believe the origin to be neoplastic. Some genetic and familial associations have also been reported. Malignant transformation is extremely rare, with only two cases reported in the literature, despite the recurrence potential. Like the etiology, the name of this entity is also controversial. Some authors prefer the term "peritoneal inclusion cyst (PCM)" instead of "benign cystic mesothelioma" and argue that the term mesothelioma should only be used when there is evidence of atypia. Most cases of BMPM are discovered incidentally. Others reflect sequela of tumor mass effect. It appears intra-operatively as large, multi-focal, cystic lesions in the peritoneal and pelvic cavity. Diagnosis is achieved through surgical sampling with histopathological examination. Immunobiologically, BMPM exhibits multiple small cystic spaces with flattened lining containing calretinin positive cells without atypical features, mitotic figures, or tissue invasion. Treatment includes cytoreductive surgery. Here we present a case of BMPM in a 60-year-old male – a rare disease in an uncommon patient population.

Keywords:
Cystic Mesothelioma, Mesothelioma, BAP1 protein, human, Asbestos, Cystic Lymphangioma.

CASE REPORT

The patient is a 60-year-old male who initially presented to the emergency department with acute onset, throbbing, episodic right flank pain, associated with nausea and hematuria. There was a concern for renal colic, and non-contrast computerized tomography (CT) of the abdomen/pelvis demonstrated a 0.6 cm calculus in the right proximal ureter causing right obstructive uropathy. An incidental 7.9 x 9.6 cm multi-lobulated cystic mass located posterior to the urinary bladder was also discovered. His nephrolithiasis was treated, and follow-up CT of the abdomen/pelvis with intravenous contrast confirmed a persistent, lobular, fluid-attenuation mass within the recto-vesical space, and additional lobular cystic lesions within the right colonic gutter (Figure 1). Ultrasound done demonstrated multi-loculated anechoic complexes with thick septations.

[a] Ascension St. John Hospital, Anatomical & Clinical Pathology. Detroit, MI, USA.
[b] Ascension ST John Hospital, Department of Pathology. Detroit, MI, USA.
[c] Ascension Providence Hospital, Department of Internal Medicine. Southfield, MI, USA.
[d] Ascension ST John Hospital, Department of Surgery. Detroit, MI, USA.

Tumor markers, including CA-125, CA19-9, and CEA, were within normal range. Subsequent laparotomy revealed mucinous appearing deposits in the peritoneal surfaces in the right lower quadrant. The appendix had adhesions to the anterior abdominal wall and was also coated with tumor deposits. Specimens were sent to pathology, and frozen sections demonstrated lesions consisting of multiple cysts, some of which are multiloculated (Figure 2).

These cysts were lined by flattened mesothelial cells, which was consistent with benign multicystic peritoneal mesothelioma. The patient subsequently received hyperthermic intraperitoneal chemotherapy (HIPEC) with tumor debulking with resection of the cystic abdominal and pelvic lesions. On histology, the surgical specimens (peritoneal nodule, mesenteric nodule, right diaphragm peritoneal nodule, left upper quadrant nodules, omentum, and pelvic cystic mass) exhibited multiple small cystic spaces with bland, flattened mesothelial lining without atypia or invasion (Figure 3).

Immunohistochemistry revealed the tumor cells to be reactive for calretinin (Figure 4), and non-reactive for Ber-EP4 consistent with benign multicystic peritoneal mesothelioma.

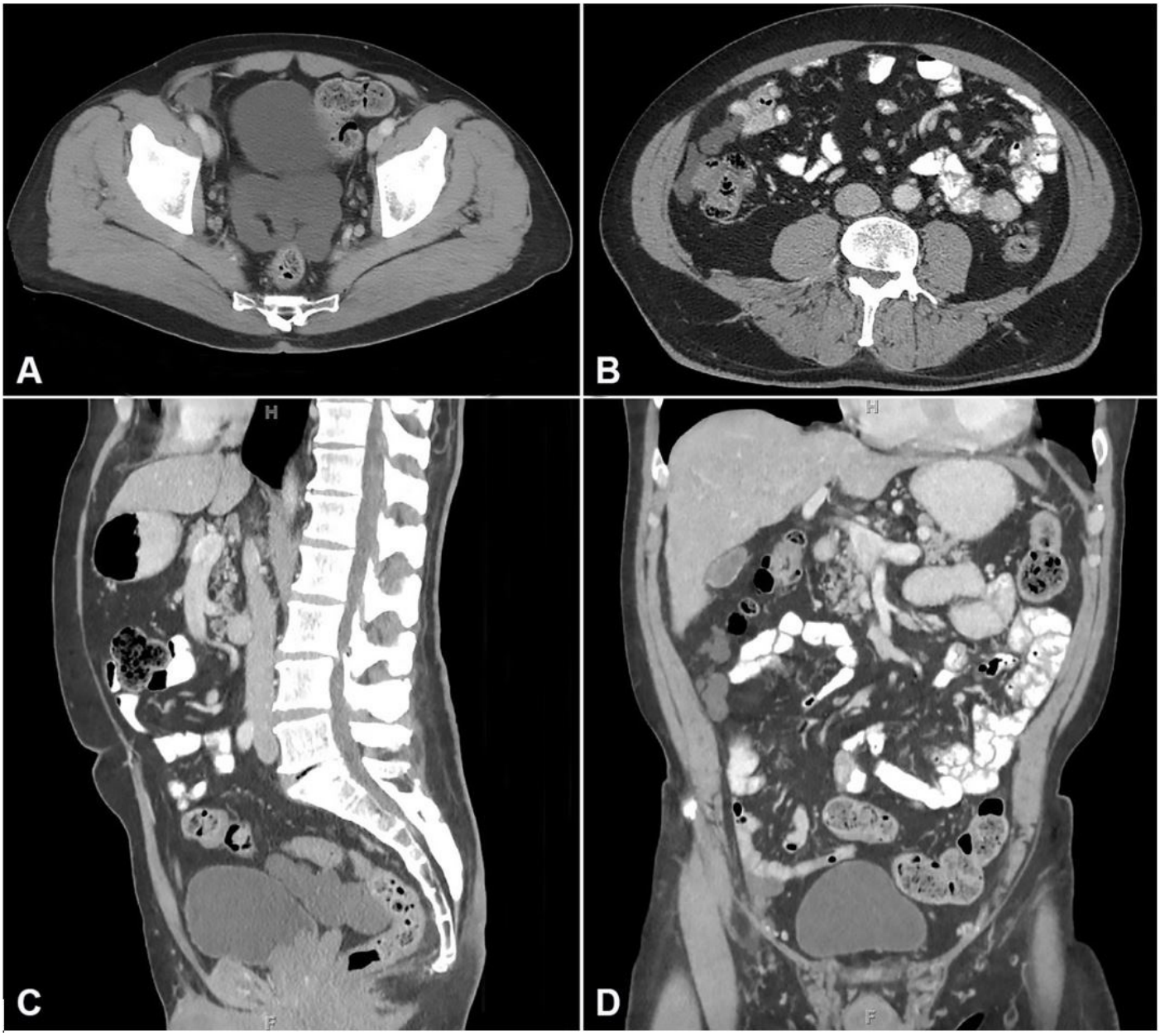

Figure 1. Abdominal contrast-enhanced CT scan of BMPM. **A** – Axial Post-Contrast CT demonstrating cystic lesion posterior to the urinary bladder; **B** – Axial Post-Contrast CT demonstrating cystic lesion in the right para-colic gutter; **C** – Sagittal Post-Contrast CT demonstrating cystic lesion posterior to the urinary bladder; **D** – Coronal Post-Contrast CT demonstrating cystic lesion in the right para-colic gutter.

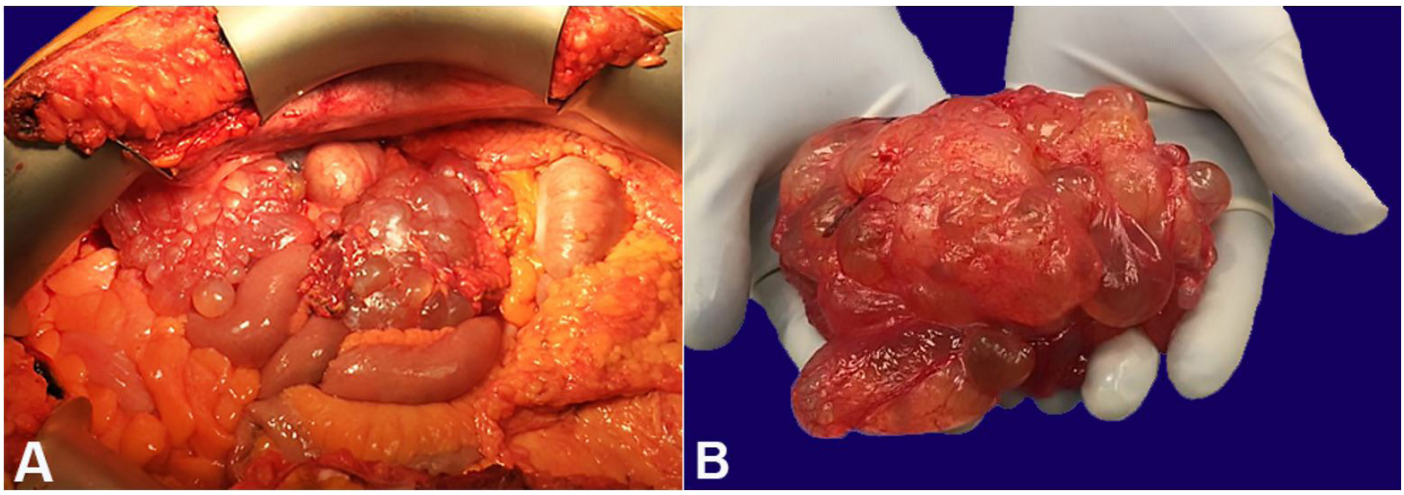

Figure 2. Intraoperative images showing multicystic, grapelike masses.

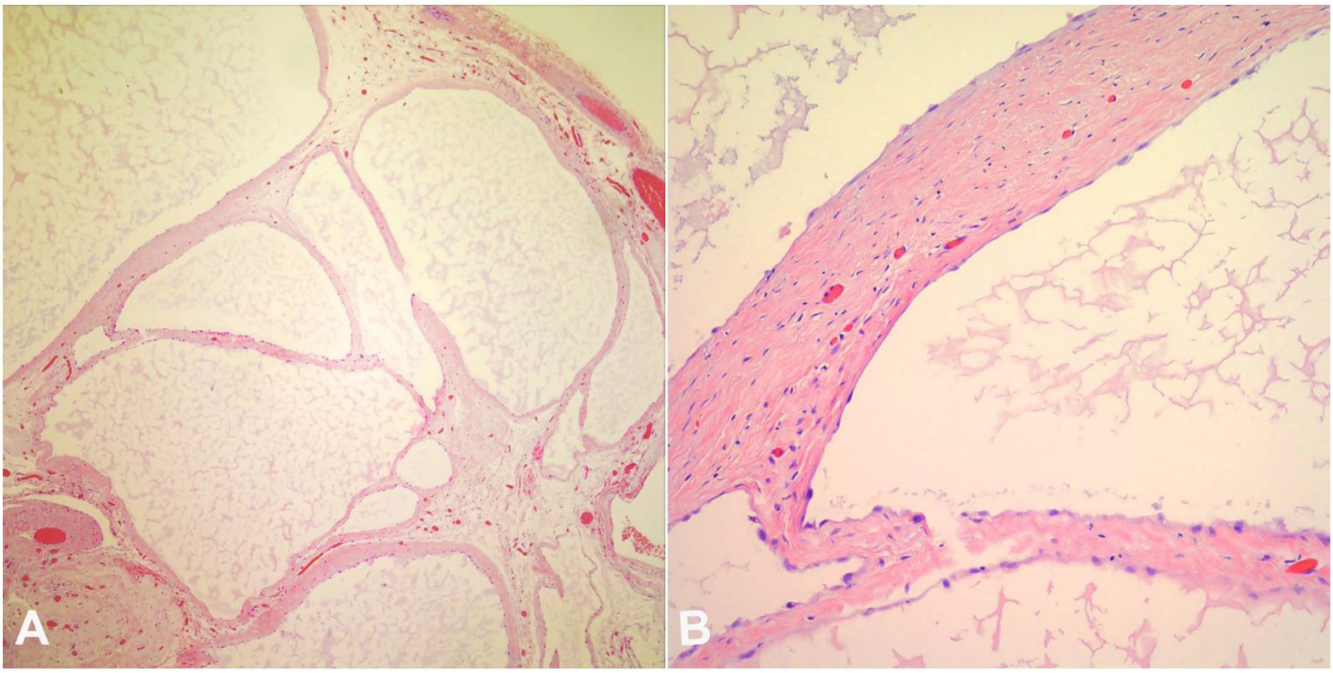

Figure 3. Photomicrograph of the surgical specimen showing in **A –** numerous variably sized cystic spaces (H&E-Low power magnification); **B** – Higher magnification showing mesothelial cells lining the cysts (H&E, 400X).

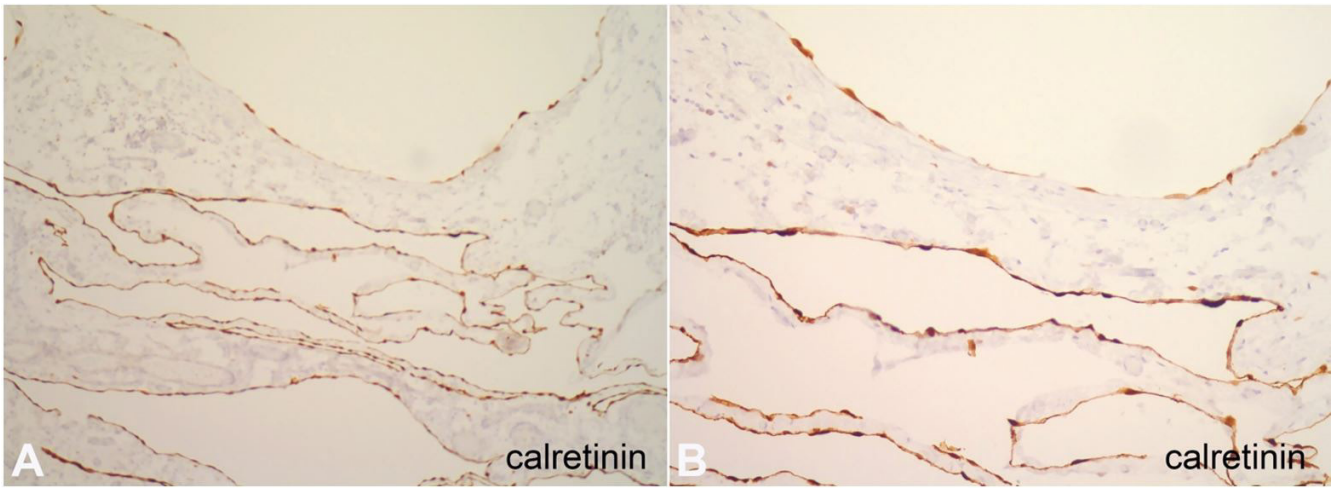

Figure 4. Photomicrograph of the surgical specimen showing in **A** and **B** – Calretinin immunohistochemical staining (×400) reveals a positive reaction.

DISCUSSION

Benign multicystic peritoneal mesothelioma (BMPM), first described by Plaut in 1928,[1] is a rare peritoneal tumor that arises from the peritoneal mesothelial cells. To date, there are less than 200 documented cases worldwide,[2] and it accounts for approximately 3-5% of the peritoneal mesotheliomas. This condition is most commonly described in women of reproductive age with a ratio of 4-5:1 female to male, with very few cases reported in females over 30 years of age.[3]

The pathogenesis of BMPM remains to be elucidated. Due to its association with pelvic inflammatory disease (PID), endometriosis, leiomyoma, and a history of previous surgery,[1,3,4] some authors believe that it has a possible reactive etiology.[5] One of the hypotheses states that chronic peritoneal inflammation triggers the proliferation and migration of peripheral mesothelial cells and associated connective tissue, giving rise to these cysts.[6] However, lack of previous surgery or inflammation in some reported cases and high recurrence rate (50-60%)[7] has led others to believe that the disease etiology is likely neoplastic. Various terms have been used to describe this entity including, multilocular peritoneal inclusion cyst, cystic mesothelioma, peritoneal mesothelial cysts, inflammatory cysts of the peritoneum, and postoperative peritoneal cysts, what shows the lack of consensus on the etiology and behavior of this entity.[3] The time between the surgery and the development of these cysts ranges from 6 months to 20 years,[8] and the relapse may occur decades after the primary surgery.[9] Recurrence occurs more frequently in large masses or disseminated disease.[10] A genetic and familial association of BMPM has been reported by a few studies. One report describes a 43-year-old man with familial Mediterranean fever, which is more commonly associated with malignant mesothelioma, who developed BMPM.[11] Another case described two female siblings with no history of prior surgery, pelvic inflammatory disease, or endometriosis and was diagnosed with BMPM.[12] Unlike pleural mesothelioma, benign multicystic mesothelioma has not been associated with asbestos exposure.[12]

Most of the cases of BMPM are diagnosed incidentally on imaging or during laparotomy for other indications. In others, the clinical presentation depends on tumor bulk and location, with large lesions causing abdominal pain, fullness, distention, intestinal obstruction, nausea, vomiting, weight loss, and/or changes in bowel habits.[4,13] Abdominal tenderness, abdominal distention, and palpable abdominal or pelvic mass may be present on physical examination. BMPM typically arise from the pelvic peritoneum but can also develop on the serosal surfaces of ovary, uterus, bladder, rectum, cul-de-sac, lymph nodes, spleen, and liver.[3,4] In women, BMPM is typically located along the peritoneal surfaces of the posterior cul-de-sac. In men, BMPM commonly develops along the peritoneal surface of the recto-vesicular pouch. Ultrasound or CT reveals multicystic masses. In our case, also the ultrasound demonstrated multi-loculated anechoic complexes with thick septations[14] and CT revealed well-defined, low attenuating, cystic abdominopelvic masses with possible enhancement.[15] Magnetic resonance imaging (MRI) shows hyperintense signals reflecting cystic fluid, with possible gadolinium enhancement of the septa.[16] In all imaging modalities, mild free-fluid and minimal peritoneal thickening may be noted – a stark contrast to malignant peritoneal mesothelioma, which frequently presents with frank ascites and diffuse peritoneal thickening. Diagnosis is achieved through surgical sampling with immunohistopathologic studies. It has also been suggested that the biologic behavior of the condition is worse in patients with high levels of CA125.[7]

Grossly, cysts in BMPM can be unilocular or multilocular. They are either free-floating in the abdominal cavity or adherent to the peritoneal structures like ovaries, bowel, fallopian tubes, appendix, omentum, and uterus. Individual cysts range from 1 mm to >1 cm. These cysts sometimes cluster and form grape-like masses in the peritoneal cavity, which can range from a few millimeters to 20 cm.[3] The cysts are either empty or contain clear or hemorrhagic fluid.

Histologically, BMPM demonstrates numerous small cystic spaces lined by a single layer of cuboidal or flattened mesothelial cells. The cysts are variably sized and often contain pale eosinophilic proteinaceous fluid. There is usually no evidence of nuclear atypia; however, sometimes cells may show bi or multinucleation with hyperchromatic nuclei that may have a hobnail, cribriform, or tufting appearance. These features exhibit complex architecture, mimicking malignant

peritoneal mesothelioma, which complicates arriving at a definitive diagnosis.[3] The loose fibrovascular stroma between the cysts often contains sparse inflammatory infiltrate with occasional lymphoid aggregates, and granulation tissue with recent and old hemorrhages. Immunohistochemical stains typically show immunoreactivity for epithelial membrane antigen (EMA), calretinin, CA125, Wilms' tumor antigen, vimentin, D2-40, and keratin. Furthermore, Ber-EP4 stain would not show immunoreactivity, thus making the diagnosis of carcinoma less likely. Some cases have shown positivity for ER and/or PR.[3]

The differential diagnosis for BMPM is wide and includes both benign and malignant lesions that present as cystic abdominal or pelvic masses. Benign lesions include cystic lymphangioma of the retroperitoneum,[8,9,17-23] cystic form of endosalpingiosis, endometriosis, Mullerian cysts, cystic adenomatoid tumors, and cystic mesonephric duct remnants. Malignant lesions, mimicking BMPM include malignant mesothelioma, serous tumors involving peritoneum, and ovarian clear cell carcinomas.[17,18]

Malignant mesothelioma (MM) is a major differential in the diagnosis of BMPM, and distinguishing benign and malignant mesothelioma is very crucial to patient care. MM is an aggressive, malignant tumor of mesothelial cells arising in pleura, peritoneum, or pericardium likely related to asbestos exposure. It can show a variety of morphologic patterns, including microglandular, tubular, and papillary growth, but is rarely cystic. Microscopic examination shows the presence of cytologic atypia and mitotic activity and infiltrating growth pattern.

Invasion is the most reliable criterion for determining that a mesothelial proliferation is malignant; however, some reactive/benign mesothelial proliferations show the entrapment of benign mesothelial cells within a fibrous stroma, which can mimic neoplastic invasion making the morphological diagnosis very difficult. Certain immunohistochemical stains like p53, EMA, GLUT-1, IMP-3, and CD146[24] are typically more positive for reactive than for malignant cases, but one cannot rely on the immunological signs to distinguish the two.[25] More recently, it is found that the loss of BRCA1-associated protein 1 (BAP1) expression is associated with malignant mesothelioma, and this helps distinguish MM from other reactive/atypical mesothelial lesions.[26,27] Several studies have shown that the homozygous deletion of *p16* by FISH is found only in malignant mesotheliomas, which is not present in benign mesothelial proliferations.[28,29] Currently, BAP1 IHC and *p16* FISH are considered to be the most effective in discriminating benign and malignant cases.[24]

Cystic lymphangioma is a benign tumor occurring in the mesentery, omentum, mesocolon, and the retroperitoneum, and ovaries mainly of children,[19] and is characterized by cystic dilatation of lymphatics that when presents in the retroperitoneum may resemble BMPM on imaging with uni or multilocular cysts.[9] Microscopic examination reveals the cysts to be lined by flattened endothelial cells and filled with chylous material with fibrotic stroma containing lymphocytic infiltrates. These can be differentiated from BMPM with immunohistochemical staining for endothelial markers: CD34, CD31, factor VIII, and VEGFR3,[18,23] which are not immunoreactive in mesothelial cells. Florid cystic endosalpingiosis can also present like BMPM when it involves the peritoneal lining and forms a mass lesion. The radiological and gross appearance of these lesions can be easily confused with benign cystic mesothelioma or even endometriotic cysts, and the histopathological examination becomes necessary for the diagnosis. Microscopically, these cysts are lined by the tubal epithelium with a variable population of ciliated cells, nonciliated secretory cells, and occasional intercalated cells.[21] The immunohistochemical analysis shows immunoreactivity for PAX8, CK7, WT1, estrogen, and progesterone receptors.[30] Adenomatoid tumor grossly and histologically resembles BMPM. It is a benign, localized proliferation of mesothelial cells that is often discovered incidentally. It is usually well circumscribed with smooth, firm, tan-yellow, and sometimes cystic cut surface. Microscopically, they are distinguished from the BMPM by the presence of a recognizable solid component along with the cystic component. The mesothelial cells are bland and may show vacuolated cytoplasm, giving a signet ring morphology. The immunohistochemical profile is similar to that of BMPM, thus differentiating the two relies on morphologic and clinical features. Mullerian cysts present grossly as large multilocular cysts, which may resemble BMPM on imaging. Microscopically, they are characterized by cuboidal to tall columnar, mucin, or serous secreting lining of nonciliated epithelium with loose fibrous tissue, dilated vessels, and

incomplete smooth muscle bundles which are usually found around the genitourinary organs or pelvis.[22,31] Immunohistochemical staining shows reactivity for paired box gene 8 (PAX8), estrogen receptor (ER), progesterone receptor (PgR) and is non-reactive for calretinin and D2-40.[31]

Treatment options range from conservative management to complete resection, followed by hyperthermic intraperitoneal chemotherapy (HIPEC). However, no consensus has yet been achieved on the standard treatment and follow-up of these patients. Some authors believe that asymptomatic patients should be followed conservatively with serial imaging,[3] and the surgical intervention should only be considered as the disease becomes aggressive. However, at the same time, there are no defined guidelines for the follow-up and interval between serial imaging of the patients undergoing conservative treatment.

Surgery is considered the mainstay of treatment by most because of its high overall recurrence rate of 50-60% after the resection, with 33% in men and 50% in women.[1] This high recurrence rate also warrants an intense surveillance schedule after the primary resection. For surveillance, some authors suggest that CT should be done every 3 months for the first year after resection and then annually for the next 5 years.[4]

In contrast to the conservative management and surgery alone, cytoreduction followed by HIPEC has also been tried by many, including our case.

Since BMPM has been shown to have a malignant potential by a few studies, some prefer cytoreduction followed by HIPEC with cisplatin and doxorubicin, including our case in contrast to conservative treatment or surgery alone. This modality is also thought to lower the recurrence rate.[4] Our patient is also in disease remission currently.

Other treatment options include laparoscopic laser ablation with potassium titanyl phosphate, and sclerosing therapy with tetracycline,[32] treatment with anti-estrogen therapy (e.g., tamoxifen), and GnRH agonists (e.g., leuprolide acetate). In one of the case studies, the recurrence was treated with cyst aspiration in one patient and hormonal treatment in the other. Both resulted in the regression of the cyst and alleviation of clinical symptoms.[29]

Like the etiology, the treatment for benign cystic mesothelioma remains controversial. There is no standard algorithm for the treatment and follow up of these patients.[14] Despite the recurrence which occurs more frequently in large masses or disseminated disease,[10] the prognosis is very good, with only one death reported in the literature.[33] Two cases have been reported to have malignant transformation.[34]

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The authors retain a signed informed consent and the manuscript is in accordance with Research ethics commission.

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Correspondence
Momal Tara Chand
Anatomical & Clinical Pathology - Ascension St. John Hospital
22101 Moross Rd – Detroit/MI – USA
PO Box: 48236
Phone: +001 (313) 343-3133 / Fax: +001 (313) 881-4727
taramomal@gmail.com