

Benign multicystic mesothelioma: a case report of three sisters

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Introduction

Benign multicystic mesothelioma (BMCM) is a rare tumor of the abdomen-peritoneum of unknown etiology.¹ This benign tumor was initially described by Plaut in 1928 when he observed loose cysts in the pelvis during a surgery for a uterine leiomyoma.² The mesothelial origin was later confirmed by electron microscopy by Mennemeyer and Smith in 1979.³ To date, there are approximately 140 cases of BMCM reported in the literature.⁴ This disease primarily occurs in pre-menopausal women and is associated with a history of pelvic inflammatory disease, prior abdominal surgery, and endometriosis.^{4,5} The pathogenesis of this disease remains controversial, with possible etiologies including a neoplastic versus a reactive process.⁵

In the literature, a few case reports discuss a possible genetic or familial association with BMCM.⁶ Specifically, one report describes a man with familial Mediterranean fever who developed BMCM. Although familial Mediterranean fever is associated with malignant mesothelioma, he had only BMCM, and did not suffer from malignant mesothelioma.⁶ A genetic evaluation and chromosomal analysis were not able to identify a specific genetic cause of the family's pattern of disease.

This case report describes two female siblings diagnosed with BMCM. In addition, a third sister also had findings consistent with BMCM, however, the discrete histological diagnosis was never confirmed.

Case #1

K.S. is a 53-year-old G3P3003 menstruating female who presented to her gynecologist with a complaint of intermittent urinary urgency. She denied symptoms of bloating, fullness, and constipation. Her gynecological history was significant for menarche at age 13 with regu-

lar menses, use of oral contraceptive pills for 5 years, and normal pap smears in her lifetime. The patient had three normal spontaneous vaginal deliveries. Her medical history was significant for hypothyroidism, which was well controlled on levo-thyroxine. Her past surgeries included a benign breast biopsy, wisdom teeth extraction, and removal of her tonsils and adenoids. Her family history was significant for a maternal grandfather who died of breast cancer in his 80's and an aunt with colon cancer.

On physical exam the patient was a thin, healthy-appearing woman. She was normotensive, with a blood pressure of 144/78 mmHg, and a body mass index of 22.8 kg/m². Her abdomen was soft with no masses appreciated. Her pelvic exam was notable for a 7 cm irregular mass in the cul-de-sac, which was non-tender and immobile.

A transvaginal ultrasound was performed that revealed bilateral ovarian masses. For further evaluation, an MRI was obtained, which revealed a multilobulated cystic structure with septations present in the cul-de-sac. CA-125 level was normal (12 U/mL).

The patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and tumor debulking to no visible residual disease. Intra-operative findings included a 14-week sized uterus with a globular contour and numerous cystic, mucoid lesions on the uterine serosa. The right ovary had mucinous, grape-like cystic structures attached. The pelvic peritoneum had mucin-like cystic masses scattered along the pelvic sidewalls as well as in the cul-de-sac. Numerous similar cystic lesions were present on the omentum at the level of the hepatic flexure, along the right lateral margin of the infracolic omentum and on the mesentery of the terminal ileum. The fallopian tubes and the left ovary appeared to be within normal limits.

Intra-operative examination revealed bilateral ovaries and fallopian tubes to have multiple cystic structures on their serosal surfaces. The cysts ranged in size from 2 mm to 4.5 cm, and were clear-walled structures containing thin, clear fluid. The cyst walls contained no papillary projections and were smooth. Many of the pelvic sidewall cystic masses that were resected were macroscopically tan-red in appearance with irregular membranous tissue. The largest of these cystic masses measured 9.0x5.0x0.2 cm. On microscopic evaluation, these cysts were lined with benign appearing mesothelial cells that were flat to cuboidal. They stained positive for calretinin immunostain further supporting the diagnosis of benign multicystic mesothelioma.

The final diagnosis was benign multicystic mesothelioma, endometriosis, and focal endosalpingiosis. The patient had an uneventful recovery and has had no recurrences one year after surgery.

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Case #2

M.S., the younger sister of K.S., was 35-years old when a pelvic mass was discovered on routine gynecologic exam. She is a G3P3003 with normal spontaneous vaginal deliveries and a surgical history significant only for wisdom teeth removal. She is a non-smoker, takes no medications, and is allergic to trimethoprim-sulfamethoxazole.

After the incidental finding of a pelvic mass, she underwent a CT scan of the abdomen and pelvis that confirmed a pelvic mass measuring 8.6x5.3x4.9 cm. It was located posterior to the uterus, extending to the cul-de-sac, and described as multicystic-appearing in nature; no free fluid or ascites were noted. The patient complained of occasional left lower quadrant discomfort. Serum tumor markers were within normal limits.

She underwent a supracervical abdominal hysterectomy with bilateral salpingo-oophorectomy and lysis of adhesions. Intraoperatively, multiple cystic grape-like structures along the pelvic sidewall, cul-de-sac peritoneum, and bladder were described. Intra-operative frozen section returned with findings of a benign multicystic mesothelioma.

The masses were tan-pink in color, polycystic, and semi-translucent on macroscopic inspection. There were multiple varied sizes of translucent "grape-like" cysts present along the ovaries and fallopian tubes bilaterally. Microscopic evaluation revealed the cystic structures to be of varying size, and lined with flat or low cuboidal mesothelial cells containing serous fluid. Multicystic nodules contained marked congested fibrovascular tissue, some with inflammatory cells with varying degrees of severity. Several of the nodules contained adenomatoid tumors.

After her surgery, the patient was started on continuous estrogen replacement therapy due to her desire to prevent estrogen withdrawal symptoms. She was then followed closely with ultrasounds and CT scans of the abdomen and pelvis. Two years after her surgery, the BMCM recurred with multiple cysts throughout her pelvis, which has been managed conservatively without further surgery. The patient remains asymptomatic, and her lesions remain stable.

Case #3

The two sisters presented above have a third sister, who, at age 46, presented to her gynecologist with a persistent left ovarian cyst. She underwent a laparoscopic bilateral salpingectomy. Intraoperatively, multiple small “blister-like” excrescences in the cul-de-sac and on the surface of the right ovary were noted. The peritoneal surfaces and omentum were found to have multiple “blister-like” excrescences. In addition, the distal right fallopian tube contained a “simple” cystic structure and the distal left fallopian tube had a multiloculated cystic structure. Intra-operative frozen section described these specimens to be benign in nature. The final pathology returned with benign mesothelial and serous cysts, hydrosalpinges, and Walthard cysts. No further staining was performed to suggest or exclude the diagnosis of BMCM. This sister remains asymptomatic and has had no further surgeries.

Discussion

Benign multicystic mesothelioma is a rare lesion that most commonly arises from the surfaces of the pelvic peritoneum. It has had several different names used in the literature due to an ongoing debate regarding its origin. Alternate nomenclature for this disease includes: peritoneal inclusion cyst, multilocular inclusion cyst, and multicystic mesothelioma.⁷ It most commonly occurs in premenopausal women with a mean age of onset of 37 years.⁸ It has been described in postmenopausal women, and 16-17% of cases have been reported in men with a mean age of onset of 47 years.^{7,9} There is no association with asbestos exposure.^{8,10}

Most patients are diagnosed incidentally either on physical exam or as a finding on imaging, or during laparotomy for other indications.¹¹ A small number of patients present with abdominal pain, distention, ascites, dysfunctional uterine bleeding, referred shoulder pain, dysuria, or dyspareunia.^{9,11} Rarely, BMCM presents as an acute abdomen.⁸ Diagnosis is

difficult as there are no reliable clinical findings, features on imaging, or tumor markers that are pathognomonic for this tumor.¹² Ultrasound and CT scan reveal cystic masses that cannot be differentiated from other pelvic pathology.

Differential diagnosis includes both benign and malignant abdominal lesions including cystic lymphangioma, endosalpingiosis, adenomatoid tumors, mesonephric duct remnants, malignant mesothelioma, sarcoma, and non-Hodgkin's lymphoma.^{8,11} Clinically, the differential diagnosis of BMCM from other ovarian tumors is important, since BMCM can be treated with ovarian preservation techniques.¹¹

The pathogenesis of BMCM remains controversial. Some believe it is a reactive process while others believe it is a neoplastic process. There is an association between prior surgeries, endometriosis, pelvic inflammatory disease, intra-peritoneal inflammation and BMCM, which suggests a possible reactive process. The hypothesis behind the reactive process pathogenesis says that chronic peritoneal irritation may react with mesothelial cell entrapment, and cause reactive proliferation and cyst formation.^{5,11} On the other hand, others believe that a neoplastic process is the cause, with a slow progressive nature and marked tendency to recur after multiple surgical resections.⁵

The tumor is usually found on the surfaces of the pelvic viscera, especially on the peritoneum of the cul-de-sac, rectum, and bladder.⁸ Macroscopically, BMCM appears as solitary or multi-septated, translucent, grape-like cysts with thin walls that are separated by fibrous tissue.^{6,8} Cyst size can vary from 1-2 mm to greater than 30 cm, and are usually multilocular.^{6,8} The cysts are either empty or filled with serous, bloody or mucinous fluid. At the time of diagnosis, the mean cyst diameter is 13 cm.⁷ In women it usually arises along the peritoneal surfaces of the uterus and rectum. In men it arises along the peritoneal surfaces of the bladder and rectum.⁷

Microscopic examination reveals cysts lined by a single layer of flattened or cuboidal mesothelial cells without atypia or mitosis.^{6,8,10} Focal reactive mesothelial changes such as hobnail-shaped cells and foci of mesothelial hyperplasia can be present.⁷ With immunohistochemical analysis, these cells stain positive for calretinin and cytokeratins, a reflection of their mesothelial origin.⁷

Treatment of BMCM primarily involves surgery, as complete resection has been shown to be the only effective treatment.⁶ Some authors have used more aggressive methods with some success such as laparoscopic laser ablation with potassium titanyl phosphate,¹³ sclerosing therapy with tetracycline, hyperthermic peritoneal infusion with cisplatin, and peritonectomy with intraperitoneal chemotherapy.^{14,15} As

recurrence is common, several investigators have proposed alternative and more conservative treatments with hormonal therapy.

Hormonal regulation of BMCM has been suggested by several authors who point to the characteristically pre-menopausal state of patients with this disease.^{16,18} Additionally, this disease rarely occurs in post-menopausal women or after bilateral salpingoophorectomy. At present, scant literature exists regarding estrogen receptor (ER) or progesterone receptor (PR) expression in BMCM. A case series by Sawh *et al.*¹⁶ found that some BMCM tumors stain positive for either estrogen or progesterone receptors, or both. They identified 17 cases of BMCM at their institution spanning over a 20 year period with sufficient clinical and pathological tissue for evaluation. Immunohistochemical staining for ER and PR were performed on all samples and among these three were identified with ER and or PR expression. One case revealed the mesothelial lining to be diffusely positive for ER only. A second case was focally positive for PR and a third case revealed the mesothelial lining to be focally positive for both ER and PR. These authors speculate that the finding of hormone receptor expression in only 3 of their 17 patients may be the result of metaplastic changes in the cells lining the cyst walls. Alternatively, immunohistochemical studies may not be sensitive enough to detect clinically relevant levels of hormone receptor expression.

Experimental treatment with anti-estrogen therapy (e.g., tamoxifen), GnRH agonists (e.g., leuprolide acetate), and intraperitoneal chemotherapy have been attempted with varying degrees of success.¹¹ Letterie *et al.*^{17,18} reported on two women with BMCM who declined surgical management in favor of medical management. The first case report describes a 17-year old woman who recurred twice after surgical intervention and was treated medically. She was started on a GnRH agonist (leuprolide), which initially caused an increase in the size of her pelvic mass as measured on ultrasound. After one month of treatment a decrease in the pelvic mass size was observed. After 6 months of treatment she began supplemental estrogen and progesterone to counteract the side effects of the GnRH agonist. Within 4 weeks an increase in mass size was appreciated and the patient once again became symptomatic. No immunohistochemical staining for estrogen or progesterone receptors were performed on the surgical specimens from her initial surgeries.

A second case described by Letterie *et al.*¹⁸ describes a pre-menopausal woman who was treated with tamoxifen. Within 4 weeks she reported a significant reduction in pelvic pain. Imaging with ultrasound confirmed a decrease in pelvic mass size. However, no tissue was obtained for histopathologic evaluation.

True prognosis of BMCM is unclear. The disease has a high recurrence rate of up to 50%.¹⁹ Time to recurrence varies from a few months to years, with an average of 32 months.¹⁰ In addition, size of lesions, site of disease, extent of disease burden and previous recurrence have not been found to be helpful in predicting future recurrences.¹⁶ It is recommended that patients be followed throughout their lifetime for recurrences.

Additionally, due to high recurrence rates, some authors regard BMCM as a borderline tumor, possibly between the realm of an adenomatoid tumor and malignant mesothelioma.⁶ There are only two case reports to date in the current literature that describe the malignant transformation of BMCM to malignant mesothelioma.⁵ One of these cases presented as both benign and malignant disease simultaneously, which makes it impossible to ascertain which came first. The second case, however, reports of a young woman who was being followed for benign disease, and after 10 years of conservative management with biopsy-proven benign disease, malignant transformation occurred.⁵

A familial or genetic association with BMCM has been rarely reported in the literature.⁶ As stated in the introduction, there are a few case reports describing the already well-known association between malignant mesothelioma and familial Mediterranean fever. However, there is another case report of a patient with familial Mediterranean fever who subsequently developed BMCM.¹ A different case report discusses two sisters both with a history of diverticulosis and cataracts who later developed BMCM. In addition to diverticulosis and early onset cataracts with retinal detachments, their family history was also significant for ovarian cancer, colon cancer, and congenital defects including renal agenesis, diaphragmatic hernia, and anencephaly.

In our case report of three sisters, there are no obvious or grossly unusual familial diseases or anomalies in their family history. Additionally, none of the sisters reported histories of the risk factors often associated with BMCM such as prior surgery, pelvic inflammatory disease or endometriosis.

In conclusion, BMCM is a rare disease with an uncertain prognosis. It has a high recurrence rate with a high likelihood for multiple medical and surgical treatments over a lifetime. The purported benign nature of this disease also remains in question. Therefore, a high level of suspicion with a lifetime of close follow-up are required for these patients. At present, our case report is one of few illustrating a possible genetic association with BMCM.

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