Malignant peritoneal mesothelioma in patients with endometriosis

Kelly J Butnor,[1] Justin Rueckert,[1] Elizabeth N Pavlisko,[2] Thomas A Sporn,[2] Victor L Roggli[2]

[1]Department of Pathology and Laboratory Medicine, University of Vermont Medical Center, Burlington, Vermont, USA
[2]Department of Pathology, Duke University Health System, Durham, North Carolina, USA

Correspondence to
Dr Kelly J Butnor, Department of Pathology and Laboratory Medicine, University of Vermont Medical Center, Burlington, VT 05401, USA; kelly.butnor@vtmednet.org

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ABSTRACT

Aims Florid mesothelial hyperplasia is known to result from endometriosis. Well-differentiated papillary mesothelioma and multiloculated peritoneal inclusion cysts have also been described in women with endometriosis. To our knowledge, peritoneal diffuse malignant mesothelioma (MM) arising in the setting of endometriosis has not been reported. The purpose of this study is to report the clinicopathological characteristics of women with MM and endometriosis.

Methods The surgical pathology files of a tertiary academic medical centre and the consultation files of one of the study authors were reviewed for cases of MM in females with and without endometriosis.

Results Six women with MM and endometriosis ranging in age from 29 to 55 years (median=45 years) were identified. All had peritoneal MM and endometriosis involving the peritoneum and/or adnexa. Five had epithelioid MM and one had biphasic MM. Two had paraoccupational exposure to asbestos. The median age of women with MM and endometriosis (44.5 years) was significantly less than the median age of cases without endometriosis (58.0 years) (p value=0.01).

Conclusions To our knowledge, this is the first report of MM in women with endometriosis. Interestingly, MM in the setting of endometriosis has only been observed in the peritoneum and not in other serosal cavities. The findings in the present study suggest that chronic serosal inflammation secondary to endometriosis may be an inducing factor in rare cases of MM of the peritoneum.

INTRODUCTION

While most cases of diffuse malignant mesothelioma (MM) are caused by asbestos exposure, a few instances of MM arising in the setting of chronic serosal inflammation have been reported.[1–8] Endometriosis, a condition characterised by the presence of endometrial tissue outside the endomyometrium, frequently causes reactive inflammatory changes when it involves the peritoneum. Florid mesothelial hyperplasia and reactive mesothelial proliferations resulting from peritoneal endometriosis have been well described in the literature.[9 10] There are also a few reports of well-differentiated papillary mesothelioma and multicystic mesothelioma (ie, multilocular peritoneal inclusion cysts) occurring in women with peritoneal endometriosis.[11–17] To our knowledge, peritoneal MM arising in the setting of endometriosis has not been reported. We detail the clinicopathological features of six cases of peritoneal MM in females with peritoneal and/or adnexal endometriosis.

MATERIALS AND METHODS

A retrospective search of a database of MM cases received in professional and medicolegal consultation by one of the authors and the surgical pathology files of Duke University Health System, Durham, North Carolina, was performed to identify cases of MM in women with endometriosis. The diagnosis of MM was based on characteristic gross tumour distribution as determined by imaging and/or intraoperative observations, as well as histological and immunohistochemical features, in accordance with the WHO classification.[18] The diagnosis of endometriosis was based on the clinical records and when pathological material was available for review, accompanying supportive histological features. For each case, available information regarding age, duration of endometriosis, asbestos exposure history and duration, presence or absence of pleural plaques and asbestosis, distribution and histological type of MM, treatment and survival were recorded. In cases with lung tissue available, analysis of mineral fibre content was performed using the sodium hypochlorite digestion technique as previously described.[19] This study was approved by the Duke University Institutional Review Board.

A two-sided, two-sample median test was used to compare the median age of MM cases with and without endometriosis. Statistical analysis was performed using SAS V.9 statistical software. Statistical significance was based on $\alpha=0.05$.

RESULTS

Six females with MM and peritoneal and/or adnexal endometriosis were identified. One case was from the surgical pathology files of Duke University Health System. The other five were from the consultative database of one of the authors, which over the last 7-year period included 231 women with MM, 86 of whom had peritoneal MM and 145 of whom had pleural MM. The five consultation cases of peritoneal MM in women with endometriosis represented 5.8% of all women with peritoneal MM in the database during that time period. The clinicopathological findings of all six cases are summarised in table 1.

The median age at the time of peritoneal MM diagnosis of women with endometriosis (44.5 years; range=29–55 years) was significantly lower than the median age of women with peritoneal MM who did not have endometriosis (58.0 years; range=20–85 years) in our database (p value=0.01). Specimen types in which the diagnosis of MM was established were as follows: hysterectomy with bilateral

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Table 1 Clinicopathological features of patients with endometriosis and peritoneal diffuse malignant mesothelioma (MM)

Case	Age (years)	Endometriosis duration	MM type	Distribution of MM	Time since MM diagnosis	Died of disease	Asbestos exposure (duration)
1	29	Diagnosed concurrently with MM	Epithelioid	Pelvic peritoneum and uterine serosa.	9 years		Father – plumber (10 years).
2	55	Diagnosed concurrently with MM	Epithelioid	Pelvic peritoneum, appendiceal and bowel serosa, mesoappendix, uterine serosa and subserosal myometrium.	12 years		Uncle – ironworker (8 years).
3	41	18 years	Epithelioid	Ovarian serosa, omentum and peritoneum.	10 years		Not identified.
4	48	5 years	Biphasic	Bowel serosa.	1 year	Yes	Not identified.
5	53	30 years	Epithelioid	Pelvic peritoneum.	3 years		Not identified.
6	37	Diagnosed concurrently with MM	Epithelioid	Uterine serosa.	4 months		Not identified.

salpingo-oopherectomy and pelvic peritoneal biopsies (case 1); hysterectomy bilateral salpingo-oopherectomy with pelvic peritoneal biopsies, appendectomy, and segmental bowel resections (case 2); hysterectomy with bilateral salpingo-oopherectomy and peritoneal and omental biopsies (case 3); omentectomy and segmental bowel resections (case 4); peritoneal biopsies (case 5); and a uterine serosal biopsy (case 6).

MM histological types included five epithelioid MM and one biphasic MM. The epithelioid MMs were characterised by one or more growth patterns: sheets, papillary structures, cords and/or tubules of tumour cells infiltrating serosal and/or omental tissue (figure 1A,B). Some cases (cases 4 and 5) featured desmoplastic stroma. In case 2, the tumour cells exhibited variable cytoplasmic clearing and cytoplasmic vacuoles containing wispy basophilic material, focally myxoid stroma with associated acute inflammatory infiltrate and focal stromal ossification. The biphasic MM (case 4) displayed an epithelioid component consisting of sheets, papillary structures, tubules and cords in a desmoplastic stroma, a sarcomatous component comprised of anaplastic spindle cells arranged haphazardly and a desmoplastic component with focal psammomatous calcifications involving bowel serosa.

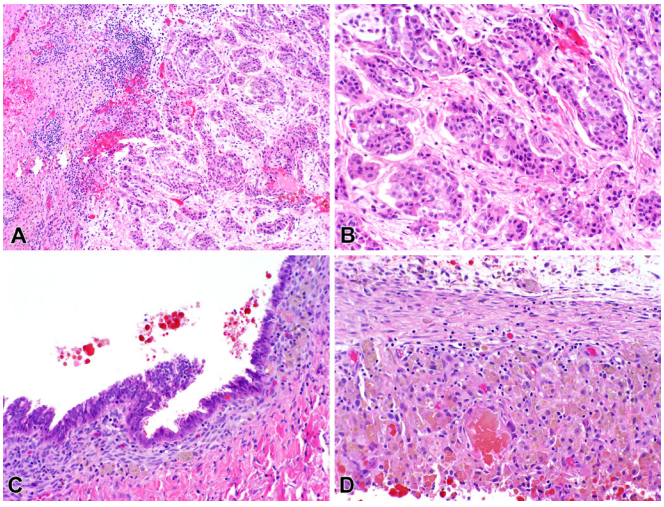

Figure 1 Thirty-seven-year-old woman with ovarian endometrioma and diffuse malignant peritoneal mesothelioma, epithelioid variant. (A) Epithelioid malignant mesothelioma that involved uterine serosa to the right of photomicrograph (not shown) invades into subserosal myometrium. (B) At higher magnification, the tumour features infiltrating tubules and tubulopapillary structures with associated desmoplasia. (C) Ovarian endometrioma featuring endometrial glands and stroma accompanied by scattered haemosiderin-laden macrophages. (D) In some areas, the ovarian endometrioma shows epithelial denudation with a lining comprised of abundant haemosiderin-laden macrophages (H&E, original magnifications ×100 (A) and ×200 (B–D)).

All of the MMs were evaluated immunohistochemically and demonstrated staining results supportive of the diagnosis, which are summarised in table 2.

Four of four cases tested were positive for pan-cytokeratin (AE1/AE3 and Cam 5.2±MNF116). All six cases were positive for the mesothelium-associated markers calretinin and D2-40, while 5 of 5 cases tested were also positive for CK 5/6 and WT-1. At least two markers typically expressed by carcinomas involving the peritoneum (CEA, BerEp4, B72.3, MOC-31, LeuM1 (CD15), PAX-8, ER and PR) were applied in five of the six cases, and with the exception of faint ER and PR immunoreactivity in case 1, no immunoreactivity for the other carcinoma-associated markers was observed. A more limited panel of carcinoma-associated markers was performed in case 6 with only weak MOC-31 staining observed.

According to available clinical records, the diagnosis of endometriosis had been established at least 5 years prior to the diagnosis of MM in three of the cases (cases 3, 4 and 5). In case 3, the diagnosis of endometriosis was made by laparoscopy and preceded the diagnosis of MM by 18 years. Endometriosis had been diagnosed in a hysterectomy and bilateral salpingo-oopherectomy specimen 5 years prior to the diagnosis of MM in case 4. In case 5, the diagnosis of endometriosis was made from an unspecified procedure 30 years before the diagnosis of MM. In case 5, there was also a history of diverticulitis. In the other three cases (cases 1, 2 and 6), the presence of endometriosis was confirmed histologically in specimens obtained during the same surgical procedure that specimens diagnostic of MM were procured. In case 1, both endometriosis and MM were present in biopsies of the pelvic peritoneum. Cases 2 and 6 exhibited ovarian endometriosis/ovarian endometrioma (figure 1C,D) that was not in direct continuity with foci of MM present elsewhere in the serosa/peritoneum. Although the diagnosis of endometriosis and MM was concurrent in these three cases, there is no way to know how long endometriosis had been present in the patients prior to the diagnosis of MM. No cases of pleural or pericardial MM arising in the setting of endometriosis were identified.

In two of the cases, there was a reported history of paraoccupational asbestos exposure (cases 1 and 2). In case 1, the woman's father was a plumber. In case 2, the woman had an uncle who was an ironworker. The husband in case 3 was a heavy equipment operator, but it was unclear whether he had exposure to asbestos. In one of the cases (case 4), lung tissue was sampled, which did not show asbestosis or a tissue asbestos content elevated above the background range for our laboratory.[20] This case also did not have pleural plaques. No lung tissue was sampled in the other

Table 2 Immunohistochemical staining results of peritoneal diffuse malignant mesothelioma in patients with endometriosis

Case	Pan-CK	Calretinin	CK5/6	D2-40	WT-1	EMA	CEA	MOC-31	BerEp4	B72.3	Leu-M1	PAX-8	ER	PR
1		+	+	+	+		–	–	–	–	–	–	f	f
2	+	+	f	+	+				–	–			–	–
3	+	+	+	+	+				–	–			–	–
4	+	+	+	+	+				–	–			–	–
5	+	+	+	+	+				–	–			–	–
6		+		+		+		w						

f, focal staining; w, weak.

five cases (cases 1–3, 5 and 6) and therefore the presence or absence of asbestos bodies or histological asbestosis could not be determined. The clinical records in these five cases were also not informative with respect to the presence or absence of pleural plaques or asbestosis radiographically.

Two of the six women were never-smokers (cases 3 and 5), two smoked ≤1 pack per day (cases 1 and 4), and the smoking status was not able to be determined from the available clinical records in the other two cases (cases 2 and 6). The clinical records were limited regarding treatment and outcome. Intra-abdominal chemotherapy was known to have been administered following the diagnosis of MM in one of the women (case 1). Her post-treatment pathological specimens showed no evidence of recurrent disease. The only woman to have biphasic MM (case 4) was known to have died of disease 1 year after diagnosis. Survival information was not available from the clinical records for the other five women (cases, 1–3, 5 and 6), but no records of them having died appeared in a search of the Social Security Death Index at 4 months–12 years following the initial diagnosis of MM.

DISCUSSION

Endometriosis is well known to cause chronic inflammation of the serosa and incite a mesothelial reaction. In some cases, mesothelial hyperplasia is so florid as to pose diagnostic difficulties by simulating a neoplastic process.[9 10] Within the spectrum of mesothelial lesions arising in association with endometriosis, a few reports of multilocular peritoneal inclusion cysts have appeared in the medical literature, as have several cases of well-differentiated papillary mesothelioma.[11–17] This is the first study to report MM arising in the setting of endometriosis. We have observed six cases of peritoneal MM, but no cases of pleural or pericardial MM, in women with peritoneal and/or adnexal endometriosis.

Interestingly, women with peritoneal MM in our database had a higher prevalence of endometriosis than has been reported in the general female population. Compared with the 5.8% prevalence of recognised endometriosis in patients with peritoneal MM in our database, the prevalence of endometriosis in general female population is estimated to be in the range of 2%–3%.[21 22] Additionally, women with peritoneal MM in our database who also had endometriosis were diagnosed with MM at a significantly younger age than those who were not known to have endometriosis. It should be noted, however, that this study was not designed to be a formal epidemiology study in which conclusions regarding the risk of women with endometriosis in the general population developing MM can be drawn. Other limitations of this study include the medicolegal consultative nature of the database and the potential bias related to possible subclinical endometriosis in the group of women without recognised endometriosis in our study population.

Overall, most cases of MM are asbestos related; however, the proportion of peritoneal MM in women that are attributable to asbestos exposure is lower.[1 23] One study of patients with peritoneal MM showed that based on lung tissue fibre analysis data, peritoneal MM in women is uncommonly asbestos-related.[24] Another study found that compared with asbestos-related MM, individuals with MM not attributable to asbestos based on fibre analysis are more likely to be young, female, have peritoneal tumours and epithelioid histology.[25] These four features were present in all of our cases except the one case with biphasic histology. In that case, there was no histological evidence of pleural plaques, and fibre analysis did not support an asbestos aetiology. The other cases reported herein lacked information regarding the presence or absence of pleural plaques and asbestosis, and while a history of paraoccupational exposure to asbestos had been documented in 2 of them, none could be conclusively attributed to asbestos.

Aside from asbestos, several other factors have been suggested as potential inducers of MM, including chronic serosal inflammation. Peritoneal MM has been reported to develop in the setting of such chronic inflammatory conditions of the peritoneum as Crohn's disease, familial Mediterranean fever-associated recurrent peritonitis and severe recurrent diverticulitis.[2 8 26–28] The mechanism by which chronic serosal inflammation induces MM is not yet fully understood, but inflammasome activation appears to play an important role.[29] Interestingly, intracellular oestrogen receptor-β, which is markedly increased in endometriotic tissue, enhances inflammasome-mediated interleukin-1β (IL-1β) production.[30] IL-1β has in turn been shown to regulate mesothelial cell proliferation.[31]

For cases not related to asbestos, a variety of factors have been postulated to induce MM, including conditions that produce chronic serosal inflammation. In this large retrospective series of MM, we identified six cases of peritoneal MM arising in women with endometriosis, a finding that has not been previously reported. No cases of pleural or pericardial MM in the setting of endometriosis were identified. The observations in this study prompt consideration of chronic serosal inflammation secondary to endometriosis as a possible inducing factor in rare cases of MM of the peritoneum.

Take home messages

- Malignant mesothelioma (MM) occurs rarely in patients with endometriosis.
- In patients with endometriosis, MM has only been observed in the peritoneum and not in other serosal cavities.
- Chronic serosal inflammation secondary to endometriosis may be an inducing factor in rare cases of MM of the peritoneum.

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