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Case Report

Diffuse Peritoneal Malignant Mesothelioma Presenting with Abnormal Uterine Bleeding: Case Report

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Mesothelioma · Malignant peritoneal mesothelioma · Pleural mesothelioma

Abstract
This report describes a highly unusual case of malignant peritoneal mesothelioma (MPM), who presented with abnormal menstrual bleeding due to diffuse infiltration of the uterus. MPM is a rare entity, which on initial clinical presentation can be indistinguishable from a primary gynecological malignancy such as ovarian cancer. As differential diagnosis is challenging among primary care physicians, gynecologists, gynecological oncologists, and pathologists, misdiagnosis and subsequent mismanagement are not uncommon. Immunohistochemical stains were required in our case to help to make the final diagnosis. We included multiple mesothelial markers such as calretinin, CK5/6, WT-1, and D240 in our analysis, in addition to epithelial markers such as Claudin-4, BerEP4, B72.3, and PAX-8, to exclude metastatic adenocarcinoma.

Introduction

Mesothelioma is a rare aggressive malignancy that can arise from mesothelial cells of the pleural, peritoneal, or pericardial lining. Most cases affect the pleura, but the peritoneum is the second most frequent site of origin of mesothelioma. Malignant peritoneal

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mesothelioma (MPM) accounts for 10–30% of all cases. The link with asbestos exposure is weaker compared to pleural mesothelioma (33–50% vs. >80%), particularly among women, but it remains the best defined risk factor. The median age at diagnosis is earlier in MPM than in pleural primaries (63 vs. 71 years). Pleural mesothelioma is more common in males, while MPM is more common in females. MPM in women also often occurs at a younger age than that in men. Furthermore, the latency period between asbestos exposure and mesothelioma development is shorter in MPM (20 years), compared to pleural mesothelioma (30–40 years) [1].

Although asbestos exposure is the predominant defined risk factor, there are also reports of MPM arising in patients who received direct peritoneal external beam radiation, but not in those who had scattered radiation from treatment to other areas. Exposure to other mineral fibers (e.g., erionite, a silicate fiber of the zeolite family) has been reported as a risk factor for peritoneal and pleural mesothelioma [2]. An association with endometriosis has also been reported [3].

The tumor suppressor gene previously identified in pleural mesothelioma, BRCA-associated protein 1 (BAP1), is frequently mutated in MPM [4], leading to the hypothesis that patients with BAP1 mutations may have a predisposition to develop malignant mesothelioma after environmental exposure to asbestos. There is some evidence that patients with BAP1 mutations have improved survival compared to those who do not carry this genetic change, an association that appears to be independent of histological type, age, and gender [2].

MPM is frequently encountered incidentally through diagnostic imaging or at the time of surgery, as symptoms can be nonspecific, the most frequent being increased abdominal girth, pain, and weight loss [5]. MPM cases have been reported in a variety of anatomical locations, such as pelvic and adnexal masses that simulate gynecological tumors, and as isolated lesions in the small intestine or omentum [6].To our knowledge, our case is only the second case [7] presented as an MPM involving mainly the uterus in a young patient, where the only symptoms presenting were heavy menstrual bleeding (HMB) and dysmenorrhea and was initially misdiagnosed as a primary uterine tumor.

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A 37-year-old Caucasian patient presented to our institution with 3 months of HMB and dysmenorrhea. She had a cesarean section for twins but had no other gynecological or surgical history. Medically, she was suffering from asthma, depression, and anxiety. Her family history was unremarkable. Her clinical examination revealed only a large and mobile uterus. Both pelvic ultrasound and computer tomography (CT) studies showed thickened endometrium and peritoneal thickening without evidence of peritoneal fluid, lymphadenopathy, or metastatic disease. The CA125 was 23 kU/L.

The patient underwent a hysteroscopy and D&C to investigate the endometrium and abnormal uterine bleeding. On hysteroscopy, a thickened endometrium was observed, but no other intrauterine pathology was apparent. A curettage was performed. Histological examination revealed a predominantly benign endometrium mixed with two small, poorly preserved fragments of the tumor. Tumor cells were epithelioid and arranged in a trabecular fashion within the fibrous stroma, showing positive staining for AE1/3, calretinin, and CD10. At the time, the tumor was interpreted as a uterine tumor similar to an ovarian sex cord tumor, a rare and usually indolent uterine tumor with low malignant potential. Therefore, the patient was scheduled for an exploratory laparotomy with preservation of the ovary, provided that the ovaries appeared macroscopically normal.

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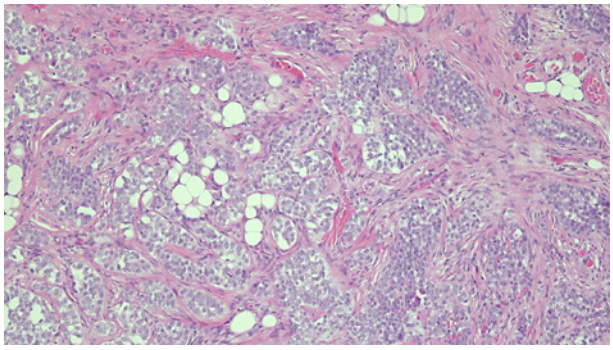

Fig. 1. Tumor resection comprising atypical epithelioid cells with prominent nucleoli within fibrous stroma at ×10. Jpg (676 KB).

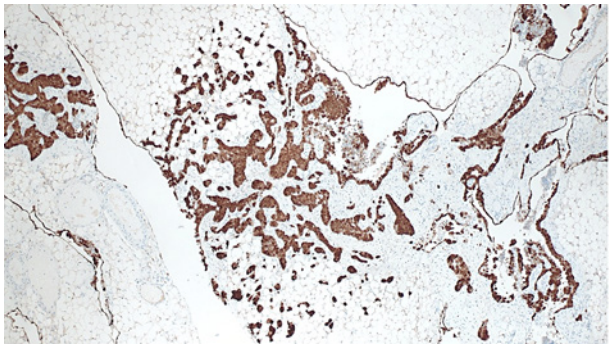

Fig. 2. Calretinin showing positive staining of tumor cells at ×4 magnification. Jpg (695 KB).

Intraoperatively, some opaque ascites and omental caking were found. There were also multiple small nodules that extended along the peritoneal surfaces of the pelvis. However, the uterus and adnexa appeared macroscopically normal. A total abdominal hysterectomy, bilateral salpingectomy, and omentectomy were performed. The patient was optimally cytoreduced to subcentimeter residual disease.

Histological examination of the hysterectomy specimen revealed patchy involvement of the uterine corpus and cervix by an apparently metastatic epithelioid malignancy. The tumor had eroded through the myometrium and endometrium, extended into the uterine cavity, and was associated with extensive lymph vascular invasion. Perineural invasion was also observed, and serosal involvement of the right fallopian tube was seen.

The primary tumor was identified within the omental resection. Microscopic examination revealed an epithelioid malignancy measuring up to 70 mm and exhibited areas of tubulopapillary, trabecular, and solid growth. Immunohistochemically, the tumor was labeled with calretinin, CK5/6, D240, CK7, and, to a lesser extent, CK20. The tumor was negative for PAX-8 and Claudin-4. Immunohistochemistry demonstrated loss of nuclear staining for BAP1. These features were indicative of MPM. ALKD5F3 was negative and MTAP was retained. The tumor showed characteristics consistent with a WHO low-grade malignancy, with only moderate nuclear atypia and no evidence of necrosis (Fig. 1, 2).

The postoperative recovery was uneventful, and the patient was discharged on day 3 after the procedure. The patient did not report a personal or family history of exposure to asbestosis when our team contacted her after the final diagnosis of MPM. After discussion at the multidisciplinary tumor board, she was scheduled for 3 months of neoadjuvant chemotherapy with cisplatin and alimta before undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The patient has given us consent to publish her case.

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Discussion

Our patient was an unusual case of diffuse MPM involving mainly the uterus and presenting with HMB and dysmenorrhea. Initially, the tumor was believed to have arisen in the uterus and initially the histopathological diagnosis of uterine tumor similar to an ovarian sex cord tumor was incorrect, a rare neoplasm, also having epithelioid morphology with some overlapping immunohistochemical features.

On CT imaging, MPM has been reported to present as solid, heterogeneous, soft tissue masses with irregular margins that enhance with the use of intravenous contrast. In our case, the preoperative CT scan showed a heterogeneous mass within the uterine cavity, which supported our initial histological diagnosis, and was in accordance with the patient's symptoms.

Elevated levels of CA125, alpha-fetoprotein, carcinoembryonic antigen, and mesothelin have been described in some patients and have been shown to correlate with disease progression. However, for diagnostic purposes, the specificity of these tumor markers has been reported to be low [5]. In our patient, only CA125 was tested and found to be normal. The definitive diagnosis of MPM was achieved by pathological evaluation of the resection specimen, which included a second opinion from a well-known pathologist with expertise in mesothelioma.

Histologically, MPM is divided into epithelioid, sarcomatoid, and biphasic subtypes. The epithelioid subtype, as present in our patient, consisted of neoplastic mesothelial cells with a resemblance to epithelium, thus mimicking carcinoma. It is the most common of the three subtypes and can display tubular, papillary, and solid growth, with these architectural patterns often admixed, as was observed in our patient. The epithelioid variant is graded on a two-tier system, which considers the degree of nuclear atypia and mitotic activity, as well as the presence of necrosis. Our case displayed moderate nuclear atypia, infrequent mitoses, and no evidence of necrosis, consistent with low-grade MPM.

MPM can be difficult to diagnose on the basis of morphology alone. Therefore, a robust and targeted panel of immunohistochemical stains is essential, ideally including multiple mesothelial markers such as calretinin, CK5/6, WT-1, and D240, in addition to a selection of epithelial markers such as Claudin-4, BerEP4, B72.3, and PAX-8, to exclude the possibility of metastatic adenocarcinoma.

It is not always easy to appreciate the malignant nature of mesothelial proliferation in MPM. However, this paradigm changed somewhat with the use of immunohistochemical staining for BAP1, as the loss of nuclear expression of BAP-1 supports a diagnosis of malignancy [8]. The homozygous deletion of *CDKN2A* by FISH also confirms malignancy. In our case, a loss of nuclear BAP-1 staining was observed. This also prompts the consideration of a possible BAP-1-associated tumor syndrome in the patient and her family.

The patient declined genetic counseling and no personal history of other BAP-1-associated tumors was obtained. Due to the rarity of MPM, there have been no randomized controlled trials on the best treatment strategies and most of the data have been based on retrospective reports of single-institution experiences. The consensus is for CRS combined with chemotherapy.

Two large multicenter studies used cisplatin, mitomycin, or doxorubicin as HIPEC agents [9, 10]. However, CRS and HIPEC can lead to significant morbidity and mortality, and in experienced institutions, the operative mortality has been reported to range between 0 and 8% and morbidity rates for serious complications between 10 and 45%. The median survival rate after CRS-HIPEC can be at least 38 months and up to 92 months [2]. For patients who are not candidates for CRS plus HIPEC, systemic chemotherapy regimens include pemetrex plus cisplatin or carboplatin or humanized anti-VEGF antibody bevacizumab [11]. This protocol is based on the studies with extensive experience in the treatment of pleural mesothelioma [12], and other authors reported a similar impact on the response rate and the median survival rate in patients with MPM [13].

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Targetable molecular pathways in MPM have also been described. There have been promising findings demonstrating anaplastic lymphoma kinase rearrangements in a small subset of patients with MPM, and the hope is that at least this small subgroup of patients could benefit from anaplastic lymphoma kinase inhibitor treatment [14]. First-generation tyrosine kinase inhibitors against the epidermal growth factor receptor have not been associated with any significant therapeutic effect in MPM. In contrast, nintedanib, an angiokinase inhibitor, has been shown to improve progression-free survival. The humanized anti-VEGF antibody bevacizumab has been reported to have promising and durable efficacy when combined to atezolizumab [15].

Conclusion

MPM is a rare malignancy with a poor prognosis. Diagnosis of MPM remains challenging and the differential diagnosis of diffuse MPM should include intraperitoneal spread of gynecological and peritoneal malignancies, as well as lymphomas, and tuberculous peritonitis.

Acknowledgments

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Statement of Ethics

Written informed consent was obtained from the patient for the publication of the details of her medical case and any accompanying histological images. Study approval statement was not required for this study in accordance with local and national guidelines.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

Funding Sources

No funding has been received for this study.

Author Contributions

All authors (I.R., T.P., and M.K.O.) have contributed to the care of the patient and to the writing of the final draft.

Data Availability Statement

All data generated and analyzed in this case report are included in this article.

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