Primary Pouch of Douglas malignancies: A case series and review of the literature

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1. Introduction

The Pouch of Douglas (POD), also known as rectouterine pouch and posterior cul-de-sac, is bordered anteriorly by the posterior uterus and posteriorly by the rectosigmoid colon. It is lined by peritoneum which originates from remnants of the Mullerian system which does not participate in organogenesis (Lauchlan, 1972). Due to the common embryology, benign and malignant lesions which mimic the Mullerian system can develop in the POD. A second mechanism for primary POD malignancies is the malignant transformation of endometriosis.

Primary POD malignancies are rare. In an extensive search of current English literature, 31 cases of primary POD malignancies were identified, with the first case reported by Dockerty et al. (1954). Mullerian types POD tumors reported include adenosarcoma, carcinosarcoma, clear cell adenocarcinoma and papillary serous carcinoma. Other tumor types reported include placenta site trophoblastic tumor, malignant meosothelioma and extragastrointestinal stromal tumor.

This paper reports 11 cases of primary POD malignancies in a single center, the largest series so far in literature.

2. Materials and methods

Patients diagnosed with primary POD malignancies from January 2006 to December 2016 were identified from the cancer registry in KK Women's and Children's Hospital (KKWCH) Gynecology department. The final diagnoses were based on intraoperative and histological findings after our multidisciplinary meeting. Intraoperatively, these tumors may be described to be located in the POD, rectovaginal pouch or rectovaginal septum. Data collected included age at diagnosis, presenting complaints, imaging studies, surgical findings, histology, treatment and progress.

3. Results

There were 11 patients identified with primary POD malignancies in the past ten years (Table 1). All of them were diagnosed in KKWCH and had subsequent treatment within the same center except for one who returned to Malaysia after primary surgery. The youngest was 24 years old at diagnosis while the oldest was 74 years old. The presenting symptoms were varied, including abdominal pain and distension, abnormal uterine bleeding, lump at introitus and reduced stool caliber. The majority were thought to have either uterine or ovarian pathology except for four whose pre-operative scans suggested POD malignancies.

Imaging modalities used included pelvic ultrasounds, magnetic resonance imaging (MRI) and computed tomography (CT). On histology post-operatively, there were seven adenocarcinomas (one unspecified, two endometrioid, one adenosquamous and three serous), two carcinosarcoma, one adenosarcoma and one perivascular epithelioid tumor (PEComa). Three patients had synchronous endometrial and POD malignancies. Four out of the seven adenocarcinomas and the adenosarcoma were found to have concurrent endometriosis as seen on histology. Five patients have died of the disease. The remaining patients have had no relapses so far at this point of writing and were disease free between 6 months to 10 years.

4. Discussion

The POD is named after the Scottish anatomist, James Douglas. It is the most dependent portion of a woman's pelvis and thus a common location for fluid, abscesses and drop metastases. Primary malignancy can also occur in the POD, albeit rare, with only 31 cases reported in English literature so far. Evaluation of a POD begins with a thorough physical examination and is aided by a variety of imaging modalities. Pelvic ultrasound is usually the imaging modality of choice to evaluate pelvic masses as it is relatively inexpensive and does not require use of a contrast agent. MRI can be valuable if the lesions need further characterization or if better delineation of soft tissues is needed to plan for surgery. However, due to rarity of primary POD malignancies and the varied presenting symptoms, POD lesions can be mistaken as lesions from ovarian or uterine origin or metastases. Case 10 (Table 1) presented with a lump in the introitus and a routine pre-vaginal hysterectomy endometrial biopsy incidentally showed endometrial cancer. The differential diagnosis based on the endometrial biopsy and the MRI finding of a POD mass was either synchronous endometrial and ovarian...
| Case no. | Age | Presenting complaint | Imaging | Preoperative diagnosisb | Intraoperative finding | Histology of POD tumor | Concurrent endometriosis | Postoperative diagnosis | Treatment | Progress |
|---------|-----|----------------------|---------|-------------------------|-----------------------|------------------------|------------------------|------------------------|-----------|----------|
| 1       | 51  | Abdominal pain       | US pelvis: 6 cm posterior cervical mass extending to lower uterine segment MRI: 8 cm mass involving left posterolateral wall of uterus | Leiomyosarcoma | POD filled with tumor | Endometrioid adenocarcinoma grade 2 | Yes | Stage II POD endometrioid cancer | Surgery (suboptimal debulking), adjuvant paclitaxel and carboplatin | Disease free 1 year 5 months |
| 2       | 48  | Prolonged menstrual bleeding | US pelvis: 0.7 cm posterior uterine wall fibroid | Endometrial complex hyperplasia, unable to exclude transformation to adenocarcinoma | 2 cm rectovaginal septum tumor | Endometrioid adenocarcinoma grade 1 | Yes | Synchronous Stage IA endometrial endometrioid adenocarcinoma and Stage II POD cancer | Surgery, adjuvant paclitaxel and carboplatin, radiotherapy | Disease free 5 years |
| 3       | 39  | Dysmenorrhea and menorrhagia | US pelvis: 2 cm posterior uterine wall fibroid | Endometrial endometrioid adenocarcinoma | 8 cm rectovaginal septum tumor | Endometrioid adenocarcinoma grade 2 | No | Synchronous Stage IA endometrial endometrioid adenocarcinoma and Stage II POD adenocarcinoma | Surgery | Unknown |
| 4       | 43  | Intermenstrual and postcoital bleeding | US pelvis: Cannot exclude underlying adenomyosis of posterior uterine wall US pelvis: 8.1 cm complex mass posterior to cervix CTAP: 8.4 cm pelvic mass arising from upper vagina/cervix | Endometrial endometrioid adenocarcinoma grade 2 | POD obliterated, friable tissue at rectovaginal septum | Adenocarcinoma Grade 2 | Yes | Synchronous endometrium endometrioid adenocarcinoma with POD tumor | Surgery, adjuvant paclitaxel and carboplatin, radiotherapy | Disease free 10 years |
| 5       | 52  | Reduced stool caliber | US pelvis: 8.1 cm complex mass posterior to cervix CTAP: 8.4 cm pelvic mass arising from upper vagina/cervix | POD mass | 5 cm rectovaginal tumor | Papillary serous adenocarcinoma grade 3 | No | Stage IIIC POD papillary serous adenocarcinoma | Neoadjuvant paclitaxel and carboplatin, interval surgery, adjuvant paclitaxel and carboplatin, radiotherapy, vault brachytherapy | DWD 4 years 10 months |
| 6       | 41  | Abdominal discomfort and mass | US pelvis: 6 cm right pedunculated fibroid 10 cm complex left ovarian cyst | Fibroid Left ovarian cyst | Caseating tumor in POD 11 cm left ovarian tumor | Papillary serous carcinoma Grade 3 Hemorrhagic ovarian cyst | No | Stage II POD papillary serous carcinoma | Surgery, adjuvant carboplatin and paclitaxel | Disease free 8 months 2 months |
| 7       | 49  | Irregular menstrual cycles, foul smelling vaginal discharge | MRI pelvis: 8.5 cm ill-defined mass in POD involving both ovaries | Metastatic ovarian carcinoma versus sarcomatous change of tissues in POD | 1 cm rectovaginal septum tumor | Serous adenocarcinoma Grade 2 | Yes | Stage IIC grade 2 POD tumor | Neoadjuvant carboplatin, interval debulking surgery, adjuvant carboplatin | DWD 3 years 7 months |
| 8       | 64  | Abdominal bloating, loss of appetite Previous THBSO for POD endometrioma at 63 years | MRI pelvis: 4.8 cm complex lesion in POD MRI pelvis: 5.4 cm complex mass in POD | POD tumor recurrence | Large pelvic tumor | Adenocarcinoma with sarcomatous overgrowth | Yes | POD adenosarcoma | Surgery (suboptimal debulking), adjuvant doxorubicin | DWD 5 months |
| 9       | 64  | Abdominal bloating Previous breast cancer at 51 years old in | MRI pelvis: 7 cm POD mass | POD tumor | 5 cm rectovaginal tumor | Carcinosarcoma | No | Stage III POD carcinosarcoma | Neoadjuvant carboplatin and paclitaxel, interval surgery | DWD 3 years 7 months |

(continued on next page)
Table 1 (continued)

| Case no. | Presenting complaint | Age a | Imaging | Preoperative findings | Histology of POD tumor | Presentative diagnosis | Treatment | Progress |
|----------|---------------------|-------|---------|----------------------|------------------------|-----------------------|-----------|----------|
| 10       | Lump at introitus   | 74 yrs | MRI pelvis: 7.5 cm mass in POD | Synchondromatous endometrial and ovarian endometrial tumor versus metastatic adenocarcinoma | Carcinosarcoma | No concurrent endometriosis | Surgery (suboptimal debulking), adjuvant doxorubicin and cisplatin | Disease free at 6 months | DWD 1 year |
| 11       | Abdominal mass      | 24 yrs | Abdominopelvic mass | CTAP: 22.5 cm abdominal pelvic mass | Malignant PEComa | Concurrent endometriosis | Surgery, suboptimal cytoreductive surgery, chemotherapy with ifosfamide and cisplatin | Disease free at 6 months | DWD 1 year |

Notes:
- a Age at diagnosis.
- b Concurrent endometriosis.
- c Depressed thickening of the uterine serosa, may also appear as leiomyosarcoma or fibroids on scans, as seen in cases 1 and 6.

The majority of the cases in this case series were Mullerian type malignancies with five out of the ten cases having concomitant endometriosis. In a meta-analysis of studies comparing endometriotic associated ovarian cancers (EAOC) to non-endometriotic associated ovarian cancers (NEAOC) (Kim et al., 2014), EAOC was associated with early stage and low grade disease. However, there were no significant differences in progression-free survival and overall survival between EAOC and NEAOC after adjusting for histology, FIGO stage and other confounding factors (Kim et al., 2014). Among the five patients with concomitant endometriosis, four of them had low to moderate grade POD adenocarcinomas and were disease free between 17 months to five years. For the patients with Mullerian type POD malignancies without concurrent endometriosis, one had moderate grade adenosquamous carcinoma, two had high grade carcinomas and two had carcinosarcomas. Two were dead with disease at 42 months and 58 months and the remaining two were disease free at 6 months and 8 years.

Mullerian adenosarcomas are mixed neoplasms composing of benign epithelial and malignant stromal (sarcomatous) components, typically arising from the uterus. While adenosarcomas are generally of low malignant potential and have good prognosis, a subgroup which exhibits sarcomatous overgrowth have higher rates of recurrence and much poorer prognosis (Carroll et al., 2014). The site of origin of adenosarcomas also affects their clinical behavior. Extragenital adenosarcomas are found to have higher rates of recurrence and mortality rates than uterine adenosarcomas (Huang et al., 2009). For the current study, two patients had carcinosarcoma of the POD. One patient had suboptimal debulking surgery and adjuvant doxorubicin and cisplatin. Unfortunately her disease was progressive and she died after 43 months. The other patient had suboptimal cytoreductive surgery and adjuvant chemotherapy with paclitaxel and cisplatin. She is disease free at six months but longer follow-up is needed.
PEComas refer to a family of mesenchymal tumors composed of perivascular epithelioid cells (Folpe, 2002) and can range from benign to malignant (Folpe et al., 2005). PEComas have been identified in multiple anatomical sites for example liver, lung and uterus among others (Selvaggi et al., 2011). Malignant PEComas are aggressive tumors with lack of effective therapies and most affected patients have poor prognosis (Starbuck et al., 2016). This current study reports the first case of POD PEComa. She was treated with surgery and six cycles of doxorubicin and ifosfamide. Her disease progressed despite treatment and died at one year post surgery.

5. Conclusion

Primary POD malignancies are rare and patients are often diagnosed with ovarian or uterine pathologies. Similar to endometriotic associated ovarian cancers, the POD malignancies with concomitant endometriosis tend to be of low to moderate grade. However more cases will need to be analyzed to verify the association. Treatment of primary POD malignancies includes primary surgery with adjuvant therapy depending on histology. With the rarer histology types, adjuvant treatment is typically based on reported cases or prior experience with the same histology types in more common sites of origin.

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