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Case series

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 mesothelioma 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 epitheliod 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

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Table 1
Cases of primary POD malignancies diagnosed in KKWCH from January 2006 to December 2016.

Case no.	Age[a]	Presenting complaint	Imaging	Preoperative diagnosis[b]	Intraoperative finding	Histology of POD tumor	Concurrent endometriosis	Postoperative diagnosis	Treatment	Progress
1	51 years	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[c]), adjuvant paclitaxel and carboplatin	Disease free 1 year 5 months
2	48 years	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 years	Dysmenorrhea and menorrhagia	US pelvis: 2 cm posterior uterine wall fibroid	Endometrial endometrioid adenocarcinoma	8 cm rectovaginal septum tumor	Endometrioid adenosquamous carcinoma grade 2	No	Synchronous Stage IA endometrial endometrioid adenocarcinoma and Stage II POD adenosquamous tumor	Surgery	Unknown
4	43 years	Intermenstrual and postcoital bleeding	US pelvis: Cannot exclude underlying adenomyosis of posterior uterine wall	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 years	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 IIC POD papillary serous adenocarcinoma	Neoadjuvant paclitaxel and carboplatin, interval surgery, adjuvant paclitaxel and carboplatin, radiotherapy, vault brachytherapy	DWD 4 years 10 months
6	41 years	Abdominal discomfort and mass	US pelvis: 6 cm right pedunculated fibroid 10 cm complex left ovarian cyst	Fibroid Left ovarian cyst	Caseating rumor 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 years 2 months
7	49 years	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 IIIC grade 2 POD tumor	Neoadjuvant carboplatin, interval debulking surgery, adjuvant carboplatin	DWD 3 years 7 months
8	64 years	Abdominal bloating, loss of appetite Previous THBSO for POD endometrioma at 63 years	US pelvis: 4.8 cm complex lesion in POD MRI pelvis: 5.4 cm complex mass in POD	POD tumor recurrence	Large pelvic tumor	Adenosarcoma with sarcomatous overgrowth	Yes	POD adenosarcoma	Surgery (suboptimal debulking), adjuvant doxorubicin	DWD 5 months
9	64 years	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.	Age[a]	Presenting complaint	Imaging	Preoperative diagnosis[b]	Intraoperative finding	Histology of POD tumor	Concurrent endometriosis	Postoperative diagnosis	Treatment	Progress
		remission								
10	74 years	Lump at introitus	MRI pelvis: 7.5 cm mass in POD	Synchronous endometrial and ovarian cancer versus metastatic endometrial cancer	8.5 cm POD tumor	Carcinosarcoma	No	Stage IIIC carcinosarcoma	Surgery (suboptimal debulking), adjuvant paclitaxel and carboplatin	Disease free 6 months
11	24 years	Abdominal mass	CTAP: 22.2 cm abdominopelvic mass	Abdominopelvic mass	20 cm tumor arising from POD	Malignant PEComa	–	Stage IIIA POD PEComa	Surgery, adjuvant doxorubicin and ifosfamide	DWD 1 year

US: ultrasound; MRI: magnetic resonance imaging; CTAP: computed tomography of abdomen and pelvis; DWD: dead with disease.

[a] Age at diagnosis.

[b] Based on clinical findings, imaging studies and/or biopsies.

[c] Optimal debulking defined as < 1 cm of residual disease.

cancer or metastatic endometrial cancer. Cases 2 to 4 presented with abnormal uterine bleeding and pre-operative diagnoses based on endometrial biopsies were endometrial hyperplasia or endometrial cancer. Their pelvic ultrasounds did not show any lesions in the POD suspicious for malignancy. POD tumors, which have invaded into 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-endometriosis 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). There are five cases of POD adenosarcomas reported in literature (Huang et al., 2009; Karateke et al., 2014). Due to the scarcity of cases, there is no consensus on optimal treatment for extragenital adenosarcomas. All five cases had primary surgery and three of them had adjuvant chemotherapy. Chemotherapy regimens included platinum based agents, ifosfamide and doxorubicin. Huang et al. (2009) reported complete response of recurrent POD adenosarcoma with sarcomatous overgrowth with doxorubicin. In this present study, case 8 who had adenosarcoma with sarcomatous overgrowth was dead with disease at five months. She had suboptimal debulking surgery and adjuvant doxorubicin. In the case reported by Huang et al., the patient had optimal debulking surgery and also had complete resection of the recurrence. Surgery is the mainstay of treatment for extragenital adenosarcomas and optimal debulking should be achieved whenever possible.

Extrauterine carcinosarcomas are very rare, with ten cases of primary POD carcinosarcomas reported in literature (Kanis et al., 2011; Ko et al., 2005; Naniwadekar et al., 2009; Shen et al., 2001; Terada, 2010). Carcinosarcomas are very aggressive tumors with poor prognosis. Due to its rarity, the treatment is often based on prior experience with uterine sarcomas. All the ten patients with POD carcinosarcomas reported in literature had primary surgeries, four with adjuvant chemotherapy, one with adjuvant radiotherapy and one with both adjuvant chemotherapy and radiotherapy. Chemotherapy regimens used included cisplatin with either ifosfamide or adriamycin or ifosfamide as single agent. Six patients were dead with disease within 12 months. The longest disease free interval was 60 months in a case reported by Ko et al. (2005), in which the patient underwent optimal cytoreductive surgery, chemotherapy with ifosfamide and cisplatin and radiotherapy. In this current study, two patients had carcinosarcoma of the POD. One had neoadjuvant paclitaxel and cisplatin with optimal interval cytoreductive surgery. 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 epitheliod 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.

References

Carroll, A., Ramirez, P.T., Westin, S.N., Soliman, P.T., Munsell, M.F., Nick, A.M., Schmeler, K.M., Klopp, A.H., Fleming, N.D., 2014. Uterine adenosarcoma: an analysis on management, outcomes, and risk factors for recurrence. Gynecol. Oncol. 135, 455–461.

Dockerty, M.B., Pratt, J.H., Decker, D.G., 1954. Primary adenocarcinoma of the rectovaginal septum probably arising from endometriosis; report of two cases. Cancer 7, 893–898.

Folpe, A.L., 2002. Neoplasms with perivascular epithelioid cell differentiation (PEComas). In: Fletcher, C.D.M., Unni, K.K., Mertens, F. (Eds.), World Health Classification of Tumorspathology and Genetics of Tumors of Soft Tissue and Bone. IARC Press, Lyon, pp. 221.

Folpe, A.L., Mentzel, T., Lehr, H.A., Fisher, C., Balzer, B.L., Weiss, S.W., 2005. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am. J. Surg. Pathol. 29, 1558–1575.

Huang, G.S., Arend, R.C., Sakaris, A., Hebert, T.M., Goldberg, G.L., 2009. Extragenital adenosarcoma: a case report, review of the literature, and management discussion. Gynecol. Oncol. 115, 472–475.

Kanis, M., Kesterson, J.P., Shroff, S., Lele, S., Mhawech-Fauceglia, P., 2011. Malignant mixed mullerian tumor of primary peritoneal origin. Ann. Diagn. Pathol. 15, 273–277.

Karateke, A., Kahramanoglu, I., Bilgic, R., 2014. Extragenital mullerian adenosarcoma in the pouch of douglas. Balkan Med. J. 31, 100–104.

Kim, H.S., Kim, T.H., Chung, H.H., Song, Y.S., 2014. Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis. Br. J. Cancer 110, 1878–1890.

Ko, M.-L., Jeng, C.-J., Huang, S.-H., Shen, J., Tzeng, C.-R., Chen, S.-C., 2005. Primary peritoneal carcinosarcoma (malignant mixed mullerian tumor): report of a case with five-year disease free survival after surgery and chemoradiation and a review of literature. Acta Oncol. 44, 756–760.

Lauchlan, S.C., 1972. The secondary Mullerian system. Obstet. Gynecol. Surv. 27, 133–146.

Naniwadekar, M.R., Desai, S.R., Ranade, R.G., Kanetkar, S.R., 2009. Extra genital heterologous malignant mixed mullerian tumor of primary peritoneal origin. Indian J. Pathol. Microbiol. 52, 88–90.

Selvaggi, F., Risio, D., Claudi, R., Cianci, R., Angelucci, D., Pulcini, D., D'Aulerio, A., Legnini, M., Cotellese, R., Innocenti, P., 2011. Malignant PEComa: a case report with emphasis on clinical and morphological criteria. BMC Surg. 11, 3.

Shen, D.-H., Khoo, U.-S., Xue, W.-C., Ngan, H.Y.S., Wang, J.L., Liu, V.W.S., Chan, Y.-K., Cheung, A.N.Y., 2001. Primary peritoneal malignant mixed Mullerian tumors. Cancer 91, 1052–1060.

Starbuck, K.D., Drake, R.D., Budd, G.T., Rose, P.G., 2016. Treatment of advanced malignant uterine perivascular epithelioid cell tumor with mTOR inhibitors: single-institution experience and review of the literature. Anticancer Res. 36, 6161–6164.

Terada, T., 2010. Carcinosarcoma in the pouch of douglas. Arch. Gynecol. Obstet. 281, 345–348.