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Case report

Cervical PEComa: Challenges in diagnosis and prognosis of a rare neoplasm

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1. Introduction

Advancements in primary human papillomavirus (HPV) vaccination, and the detection of cervical dysplasia and carcinoma using HPV DNA-based testing, cytology, and colposcopy, have led to a global decline in the incidence and mortality of cervical cancer (Kudela et al., 2016). However, these methods have decreased sensitivity for glandular histologies, HPV-independent, and rare cervical neoplasms (Kudela et al., 2016). Thus, maintaining a degree of diagnostic suspicion for "zebras," and developing a rational approach to recognizing and managing rare tumors remains important.

We present a case of a rare cervical perivascular epithelioid cell neoplasm (PEComa), with only 22 previously reported in the literature (Mateva et al., 2019; Bennett et al., 2018). PEComas are mesenchymal neoplasms with the potential for both benign and malignant behavior (Kudela et al., 2016), and were first described in 1943 by Apitz et al. in relation to renal angiomyolipomas (Kudela et al., 2016). The aim of this case report is to provide a pragmatic framework for the management and future investigation of these rare tumours.

2. Case presentation

A healthy 37-year-old G5P3 presented to her gynecologist with one year of intermittent postcoital bleeding. She previously reported regular monthly menstrual cycles. Her last Pap test was normal three months prior, with no past history of cervical dysplasia. On past medical history, she was healthy, taking no regular medications, and had two vaginal deliveries and one cesarean delivery. She reported smoking 5–6 cigarettes per day for the last two years.

On pelvic examination, her gynecologist described a friable cervical lesion. Punch biopsy was performed, and the initial pathologic report favored a benign reactive process. However, gynecologic pathology review raised the possibility of an atypical epithelioid mesenchymal proliferation extending to the biopsy margin. The differential included perivascular epithelioid cell tumor or an epithelioid smooth muscle neoplasm.

The patient was subsequently referred to colposcopy. Re-biopsy was indeterminate for dysplasia, favoring reactive atypia versus a low-grade squamous intraepithelial lesion. Endocervical curettage showed benign endocervical fragments. The colposcopic impression was an atypical cervical fibroid, and an excisional biopsy was recommended.

She returned ten weeks later for excisional biopsy of the cervix. This pathology returned as perivascular epithelioid cell tumour (PEComa) with maximum contiguous diameter 9 mm and positive peripheral and deep resection margins. She was referred to Gynecologic Oncology.

2.1. Management by gynecologic oncology

When seen in consultation at the tertiary Gynecologic Oncology centre, physical examination did not reveal any peripheral

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lymphadenopathy. On speculum examination, there was a residual erythematous and friable lesion at 12o'clock on the cervix. Bimanual examination confirmed a 2 × 1 cm firm nodule at 12o'clock on the cervix. Pelvirectal examination did not reveal any evidence of parametrial or rectal involvement. On initial bloodwork, hemoglobin was 12.3 g/dL and creatinine was 62 umol/L. No diagnostic imaging was performed preoperatively. The patient did not desire fertility preservation.

She underwent a laparotomy, modified radical hysterectomy, and bilateral salpingectomy six months after her initial presentation to her general gynecologist. Intraoperatively, there was a 1.5 cm erythematous tumour at 12o'clock on the cervix, a bulky 12-weeks' sized uterus, and normal ovaries (left in situ) (Fig. 1). A satisfactory parametrium was obtained with 1.5 cm gross vaginal margin. No additional staging or nodal assessment was performed. Her postoperative course was uncomplicated and she was discharged home postoperative day 2.

2.2. Pathologic findings and outcome

On final pathology from the hysterectomy specimen in this case, residual PEComa measured 4 and 8 mm respectively in 2 of 17 cervical sections. Infiltrative borders were present, but there was no evidence of severe nuclear atypia, necrosis, lymphovascular invasion, hypercellularity, nor mitoses exceeding 1/50 HPF. The sum of the tumor diameter based on the original resection plus the hysterectomy was less than 5 cm. Immunohistochemistry was positive for vimentin, desmin and ER with patchy positivity for HMB45, melan-A and caldesmon and negativity for CD10, WT1, SMA and CD45 (Fig. 1).

Multidisciplinary conference including pathologic review of her biopsy, resection, and hysterectomy specimens, yielded the opinion that

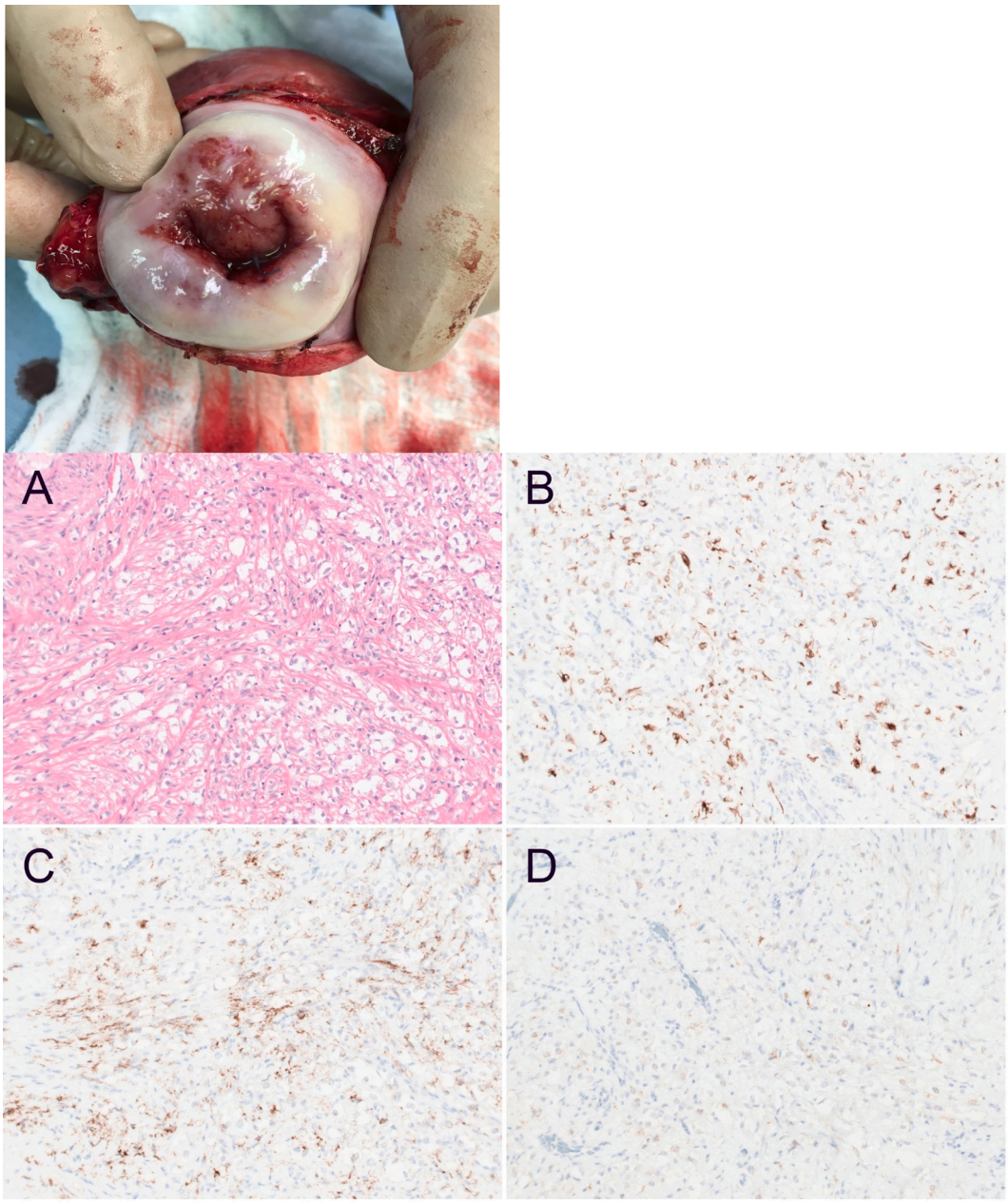

Fig. 1. Cervical perivascular epithelioid cell tumour (PEComa). Surgical specimen post radical hysterectomy showing the ectocervix including perivascular epithelioid cell tumour (PEComa). (A) Hematoxylin and eosin stained histologic section showing a tumour made of large polygonal cells with clear to granular cytoplasm and well-defined cell borders. Immunohistochemical stains are positive for desmin (B) and HMB45 (C), weakly/focally positive for MelanA (D) and negative for pankeratin (not shown).

her PEComa was classified as benign and did not require additional treatment. She was discharged for surveillance by her family physician. She remains alive with no evidence of recurrence at four years.

3. Discussion

Perivascular epithelioid cell neoplasms (PEComas) are mesenchymal tumours composed of histologically distinctive perivascular epithelioid cells. (Kovac et al., 2018; Thway and Fisher, 2015) The most common site of gynecologic PEComa is the uterine corpus (Thway and Fisher, 2015). Cervical PEComa is rare; subsequent to the review of 14 cases previously described by Mateva et al. (Mateva et al., 2019), there has been one report of a benign 4 cm cervical PEComa treated with local excision in a 45 year-old (Sharmila et al., 2021), seven cases nested within a larger case series of uterine corpus PEComas (Bennett et al., 2018), and the present case. The median age of diagnosis is 44 years (Folpe et al., 2005), and they commonly present as friable, dark-red masses with irregular vaginal bleeding or abdominal pain (Kudela et al., 2016; Kovac et al., 2018; Bradshaw et al., 2010; Celik et al., 2018; Natella et al., 2014). Establishing the diagnosis of PEComa preoperatively is often elusive; they are not reliably detected on routine cervical cytology or known to be associated with HPV (Kovac et al., 2018; Bradshaw et al., 2010; Celik et al., 2018; Zhang et al., 2013), and there is no associated serum tumour marker (Kudela et al., 2016; Natella et al., 2014). Preoperative imaging is also unreliable as they mimic leiomyomas, sarcomas or even polyps on ultrasound, CT or MRI (Kudela et al., 2016). The classic immunophenotype of PEComa involves co-expression of melanocytic markers (HMB45 and Melan A being the most sensitive) and smooth muscle markers including actin in 80 % and desmin in 30 % (Thway and Fisher, 2015; Folpe et al., 2005). Thus, these neoplasms are particularly challenging to distinguish from smooth muscle tumours (Bennett et al., 2018), and may also be misdiagnosed as clear cell sarcomas, melanomas, GISTs, and alveolar soft part sarcomas. An approach to differentiating these neoplasms using immunohistochemistry is outlined in Table 1 (Mateva et al., 2019). There is a known association in approximately 9 % of PEComas with tuberous sclerosis complex (TSC) (Folpe et al., 2005); mutations of TSC1 or TSC2 lead to loss of negative regulation of mTORC1 with resulting activation of the mTOR pathway (Kudela et al., 2016; Thway and Fisher, 2015). MTOR inhibitors have been shown to have some activity in the treatment of AML, LAM, and metastatic PEComa, including in one case arising from the cervix (Wagner et al., 2010).

The original 2005 Folpe classification originated from clinicopathologic study of 26 PEComas, with malignant tumours having ≥ 2 adverse prognostic features including tumour size (>5cm), infiltrative growth pattern, high nuclear grade and cellularity, necrosis, lymphovascular invasion, and mitoses $>$ 1/50 HPF (Folpe et al., 2005). Schoolmeester et al. in 2014 modified the classification to define malignant tumours as those with ≥ 4 adverse features (Schoolmeester et al., 2014). Notably, there were only 2 cases of cervical PEComa in the Folpe classification study (Folpe et al., 2005), and none in the Schoolmester report (Schoolmeester et al., 2014). Thus, the ability of the pathologic malignant classification to accurately predict adverse clinical behaviour in cervical PEComa, including metastatic disease or locoregional recurrence, needs further study. As shown in Table 2, 7 of 23 published cases of cervical PEComa were classified by Folpe criteria as malignant (Bennett et al., 2018; Zhang et al., 2013; Wagner et al., 2010). However, only 4 of 7 (57 %) of cervical PEComas classified as malignant by Folpe criteria demonstrated clinically malignant behaviour, with 3 of 7 (43 %) presenting or recurring with extrapelvic metastatic disease, and 1 of 7 (14 %) experiencing local or regional nodal recurrence after surgery. In contrast, there have been 111 reported cases of uterine corpus PEComa to date (Mateva et al., 2019; Bennett et al., 2018; Conlon et al., 2015), with 42 classified as malignant by Folpe criteria (Mateva et al., 2019; Bennett et al., 2018). Of these, 81 % behaved aggressively: 71 % developed extrapelvic metastases, and 10 % experienced locoregional recurrences. With the limited number of cervical PEComas reported to date, we found no significant difference in the proportion of cervical vs. uterine PEComas classified as malignant by Folpe criteria which exhibited aggressive behaviour (Fisher's exact test, $p = 0.18$). Overall, 17 % of all reported cervical PEComas (4 of 23 cases) demonstrated aggressive behaviour, compared to 31 % (34 of 111 cases) of uterine corpus PEComas; the rate of death attributed to a cervical PEComa diagnosis is 8.7 % (2 of 23 cases) (Bennett et al., 2018; Wagner et al., 2010) vs. 10.8 % in uterine corpus PEComa (12 of 111 cases) (Mateva et al., 2019; Bennett et al., 2018).

The adverse pathologic features which most frequently contributed to the Folpe malignant classification of cervical PEComas included size in 86 %, and infiltrative growth pattern, necrosis, or high nuclear grade in 71 % (Table 2). However, tumor size was the most important feature in identifying the risk of malignant behaviour in cervical PEComas, with all clinically aggressive cases measuring between 6 and 12 cm (Mateva et al., 2019; Natella et al., 2014; Wagner et al., 2010; Liu et al., 2014). In contrast, the 14 cervical PEComas with benign clinical behaviour all measured $\leq$ 4 cm (Mateva et al., 2019; Bennett et al., 2018; Sharmila et al., 2021). Interestingly, this may not be true for uterine corpus PEComas; Bennett et al.'s largest single-institution series of uterine PEComas described one aggressive uterine PEComa with distant metastases measuring 4 cm, while 21 % (3 of 14) clinically-benign uterine PEComas measured between 6 and 8 cm (Bennett et al., 2018). Tumor size may also be helpful to determine the best surgical approach in cervical PEComas. In the absence of a clear proven benefit for the use of adjuvant therapy, surgical excision with clear margins is the cornerstone of therapy for PEComas (Kudela et al., 2016; Celik et al., 2018), Of 13 cases of cervical PEComa with benign Folpe classification and reported follow-up, including ours, all but one patient who died of other causes remained alive and disease-free at between 2 and 48 months of follow-up, regardless of treatment approach (Mateva et al., 2019; Bennett et al., 2018). Treatment of these cases included trachelectomy, simple hysterectomy, modified radical hysterectomy, and adjuvant radiation

Table 1
Distinguishing pathologic factors between PEComa and related entities (Kudela et al., 2016; Bennett et al., 2018; Kovac et al., 2018; Bradshaw et al., 2010; Natella et al., 2014; Liu et al., 2014).

	HMB45	Melan A	Smooth Muscle Actin (SMA)	Desmin	S-100	Other Immunohistochemical and Molecular Features
PEComa	+	+	+ in 80 %	+ in 30 %	Less frequent	TFE3 rearrangement reported RAD51B rearrangement reported
Epithelioid smooth muscle tumours (epithelioid leiomyosarcoma)	–	–	+			Vimentin +
Clear Cell Sarcoma		+	–		+	
Metastatic melanoma		+	–		+	Vimentin +
Gastrointestinal stromal tumour		–				CD34 + CD117 +
Alveolar soft part sarcoma		–				TFE3 rearrangement

Table 2
Prevalence of Folpe's high-risk pathologic criteria in cervical and uterine PEComas with malignant behaviour (metastatic disease at presentation or recurrence, or local or regional nodal recurrence).

Folpe High Risk Pathologic Features	Cervical PEComa classified as "Malignant" by Folpe (Mateva et al., 2019; Bennett et al., 2018; Natella et al., 2014; Zhang et al., 2013; Wagner et al., 2010; Liu et al., 2014) (N = 7 of 23 total reported cases)		Cervical PEComa with extrapelvic metastatic disease at presentation or recurrence (Bennett et al., 2018; Wagner et al., 2010 (N = 3 of 23 total reported cases)		Cervical PEComa with local or regional nodal recurrence (Liu et al., 2014) (N = 1 of 23 total reported cases)		Uterine corpus PEComa classified as "Malignant" by Folpe (Mateva et al., 2019; Bennett et al., 2018) (N = 42 of 111 total reported cases)		Uterine corpus PEComa with extrapelvic metastatic disease at presentation or recurrence (Mateva et al., 2019; Bennett et al., 2018) (N = 30 of 111 total reported cases)		Uterine corpus PEComa with local or regional nodal recurrence (Mateva et al., 2019; Bennett et al., 2018) (N = 4 of 111 total reported cases)	
	N	%	N	%	N	%	N	%	N	%	N	%
Size > 5 cm	6	85.7 %	3	100.0 %	1	100.0 %	32	76.2 %	28	93.3 %	4	100.0 %
Necrosis	5	71.4 %	2	66.7 %	1	100.0 %	26	61.9 %	18	60.0 %	4	100.0 %
Mitotic rate ≥ 1/50HPF	4	57.1 %	2	66.7 %	0	0.0 %	28	66.7 %	18	60.0 %	4	100.0 %
High-grade nuclear features	5	71.4 %	2	66.7 %	0	0.0 %	23	54.8 %	17	56.7 %	3	75.0 %
Infiltrative	5	71.4 %	2	66.7 %	1	100.0 %	22	52.4 %	15	50.0 %	2	50.0 %
Lymphovascular invasion	1	14.3 %	0	0.0 %	0	0.0 %	11	26.2 %	8	26.7 %	2	50.0 %

(Bennett et al., 2018; Kovac et al., 2018; Bradshaw et al., 2010; Celik et al., 2018). This is consistent with Bennett et al.'s case series in which all uterine corpus PEComas classified as benign by Folpe criteria were alive and without evidence of disease at last follow-up (Bennett et al., 2018).

Thus, we propose that for smaller cervical PEComas (≤4cm), a cone biopsy be performed as the initial step to aid in diagnosis and determine if high-risk histologic features can be readily identified which may be missed with smaller, less representative biopsies. In their absence, conservative surgery with extrafascial hysterectomy may be adequate. This approach is supported by data from the recent ConCerv (Schmeler et al., 2021) and SHAPE trials (Plante et al., 2023), highlighting the utility of cone biopsy to select candidates for conservative surgery (Schmeler et al., 2021) in low-risk early-stage cervical cancers (Schmeler et al., 2021; Plante et al., 2015), although rare and non-HPV related histologies were not included in these trials. If pathologic features are present which indicate a greater risk of malignant behaviour, or the tumour is ≥5 cm, surgery may be tailored to ensure adequate clear margins, favouring a more radical approach.

The role of additional staging procedures in cervical PEComa has not previously been defined (Mateva et al., 2019). Pelvic nodes were surgically evaluated in only five cases of cervical PEComa (Mateva et al., 2019; Folpe et al., 2005; Bradshaw et al., 2010; Stone et al., 2013; Azad et al., 2006), four of which were classified as benign, and all were node negative. The only reported case of nodal involvement in cervical PEComa involved a 9 cm malignant PEComa initially confined to the cervix, which was treated twice with local resection and subsequently recurred in the pelvic nodes (Liu et al., 2009). Thus, pelvic lymph node assessment may be considered in PEComas classified as malignant. There is no published evidence regarding the safety or utility of sentinel node (SLN) protocols in PEComa, however there is no reason to suggest that SLN accuracy would be substantially different.

There is also limited evidence regarding the safety of ovarian preservation in premenopausal patients with PEComas. Among 42 reported cases of uterine corpus PEComas with malignant classification (Mateva et al., 2019; Bennett et al., 2018), seven (16.7 %) had ovarian involvement at presentation; in the present review of 16 cases of cervical PEComa, only one had epithelioid cellular aggregates termed by the authors as "PEComatosis" involving the ovarian hila, myometrium and small bowel lamina propria (Fadare et al., 2004). Thus, in our premenopausal patient with no evidence of extrauterine disease, we did not recommend oophorectomy. We advocate for individualized, patient-centered decision-making, with consideration of the limited evidence regarding the risk and impact of ovarian metastases, and the implications of premature iatrogenic menopause.

As with many rare cancers, the evidence is unclear regarding the benefit of systemic treatment or radiotherapy in advanced or recurrent PEComa (Natella et al., 2014), due to varied treatment approaches, few reported cases, and limited follow-up (Liu et al., 2009). Bonetti et al. reported a case of uterine PEComa initially treated with surgery involving the vagina, and pelvic and inguinal nodes, treated with adjuvant doxorubicin and ifosfamide followed by radiation for suspected residual disease (Bonetti et al., 2001). Ten months after completing adjuvant therapy, the patient recurred both locally and in the lungs and vertebrae (Bonetti et al., 2001). In contrast, Jeon et al. reported a pediatric patient with uterine PEComa with nodal metastases who received neoadjuvant vincristine, ifosfamide, and doxorubicin with stable disease, followed by hysterectomy, node dissection and adjuvant chemotherapy and radiation. The patient had no evidence of recurrence at 1.5 years of follow-up (Jeon, 2005). Future therapeutic approaches may include targeted therapies including inhibition of the mTOR pathway; case reports of neoadjuvant and postoperative sirolimus have indicated initial partial responses or disease stability, although disease progression is usually observed (Wagner et al., 2010). Next generation sequencing of these rare tumours may both facilitate development of molecular-based prognostication, and identify future therapeutic targets. Long term surveillance is recommended for early detection and management of delayed recurrence. (Celik et al., 2018; Natella et al., 2014).

4. Conclusion

Cervical PEComas are rare and challenging to diagnose, but may behave similarly to their counterparts in the uterine corpus. Tumor size is an important pathologic and clinical prognosticator, and we propose that small tumours ≤ 4 cm may be initially assessed with cone biopsy, with consideration for extrafascial hysterectomy in the absence of high-risk pathologic features, as benign Folpe classification appears to be predictive of clinically benign behaviour. While inhibition of the mTOR pathway may be a promising target for future therapy, more effective treatments are needed to treat patients with metastatic disease. This may be realized in future with systematic molecular characterization of emerging cases to identify novel therapeutic targets, and linkage with international coordinated registries that study rare cancers.

Written informed consent was obtained directly from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Dr. Sarah J. Mah: conceptualization, data curation, performed analysis and literature review, writing – original draft and editing. Dr. Mark Carey: conceptualization, contributed analysis tools, manuscript writing – review and editing. Dr. Lien Hoang: contributed data and analysis tools, manuscript writing – review and editing. Dr. Sarah Finlayson: data curation and analysis and writing- review and editing. Dr. Shaina Lee: data curation and analysis and writing- review and editing.

Conflict of Interest, Funding, and Consent Statement

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Written informed consent was obtained directly from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Sarah J. Mah: Conceptualization, Writing – original draft. **Lien Hoang:** Writing – review & editing. **Shaina Lee:** Data curation, Writing – review & editing. **Sarah Finlayson:** Data curation, Writing – review & editing. **Mark S. Carey:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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