

Case report

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# Rare malignant peripheral nerve sheath tumour of the endocervix masquerading as a leiomyoma



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#### 1. Introduction

Endocervical masses are common presentations in gynaecological clinics. This case report describes a patient with an endocervical mass thought to be a prolapsed leiomyoma but was eventually diagnosed as Malignant Peripheral Nerve Sheath (MPNST). MPNST presenting as a gynaecological mass is extremely rare, with fewer than 20 cases reported (Sangiorgio et al., 2018).

Leiomyomas are benign smooth muscle tumours. They may grow in any organ, but are commonly seen in the uterus. Conversely, MPNSTs are a rare type of sarcoma originating from the neural sheath of peripheral nerves. They are associated with genetic conditions such as Neurofibromatosis type 1 (NF1) which account for 50% of such patients (Anghileri et al., 2006). However, this association is not evident in gynaecological MPNSTs (Sangiorgio et al., 2018). MPNSTs tend to occur in major nerve trunks such as the brachial plexus, sacral plexus or sciatic nerve. Thus, it is not a common differential in gynaecological patients (Monsal et al., 2019:). Prognosis is poor with high recurrence rates despite extensive surgical and adjuvant therapy due to the aggressive nature of MPNST (Anghileri et al., 2006).

#### 2. Case description

A 37-year-old female, para 1, presented in April 2019 with profuse vaginal bleeding of 1-day duration. This was associated with lower abdominal pain and symptoms of anaemia. Her menses was previously regular without abnormal bleeding patterns. Her cervical smear performed in 2017 was normal.

She had a significant past surgical history of a Transcervical Resection of Myoma (TCRM) performed in August 2018 in Philippines. A pelvic ultrasound then showed a  $7.1 \times 5.3 \times 6.0$  cm hypoechoic structure with a 1.5 cm pedicle, suggestive of a prolapsed submucosal leiomyoma. Due to its large size, it was only partially resected during her TCRM. Final histology reported a smooth muscle tumour of uncertain malignant potential (STUMP). However, she defaulted subsequent follow-up in Philippines.

On examination, there was no palpable abdominal mass. Pelvic examination revealed a large 5 cm mass with a thick base prolapsing

through her cervix and into the vagina.

Pelvic ultrasound showed a  $9.1 \times 8.4 \times 6.8$  cm hypoechoic mass with internal vascularity occupying the lower uterus, endocervical region and extending down to the upper vagina. No vascular stalk was demonstrated between the mass and endometrium. Pelvic Magnetic Resonance Imaging (MRI) showed a  $10.4 \times 8.1 \times 9.5$  cm well circumscribed lobulated mass distending the endocervical canal and extending to the vagina with areas of focal haemorrhage (Fig. 1). Small pelvic lymph nodes measuring up to 7 mm were also seen.

The patient was counselled for definitive surgery in view of the large mass, abnormal uterine bleeding and past history of STUMP. A Total Hysterectomy Bilateral Salpingectomy (THBS) with frozen section was performed in May 2019.

Intraoperatively, a 10 cm endocervical mass was found distending the entire uterine isthmus up to the Pouch of Douglas and ballooning into the cervix (Fig. 2). The rest of her uterus, bilateral fallopian tubes and ovaries appeared normal. No obvious local invasion was seen from the mass into its surrounding structures. Peritoneal survey was unremarkable with no ascites seen and no enlarged lymph nodes. Frozen section showed low grade myxoid spindle cell tumour with atypia, suggestive of STUMP. Resection of the mass was complicated with friable surrounding tissues causing irretractable bleeding and no obvious plane seen at the right side of the vault. Decision was made to close the vault with remnant tumour in-situ.

Grossly, the excised mass had roughened surface margins with focal areas of haemorrhage. Cut-section revealed a white, firm homogenous appearance (Fig. 2). Microscopically, the tumour cells showed varied morphology of both ovoid and spindle types. Cytological atypia including elongated nuclei, inconspicuous to small nucleoli, fine chromatin and small amount of pale eosinophilic cytoplasm was seen along with a mitotic rate of up to 20 mitotic figures (Fig. 3A). Multifocal immunopositivity for S100 and C34 including patchy positivity for CD10 was also seen. (Fig. 3B).

Final histology confirmed a Grade 2 MPNST endocervical fibroblastic type within the endocervical tissue. Tumour board discussion suggested further radiotherapy before completion surgery to resect the residual tumour and complete cancer staging. However, the patient was keen for upfront surgery.

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Fig. 1. MRI Pelvis (Sagittal and Transverse Views) Demonstrating Relationship Between Mass and Uterus.



Fig. 2. Intraoperative Findings: Illustration (Sagittal and Coronal Views) with Gross Specimen.



Fig. 3. A: Spindled Cells with Cytological Atypia - Pleomorphism, Nuclei Variation and Mitosis (Arrowed) and B: Positive Immunohistochemistry Staining for S100.

Debulking surgery in August 2019 found residual tumour measuring 4.5 cm at the right vaginal vault, with a separate 1 cm nodule at the left vaginal vault. Histology confirmed MPNST with translocation-associated Neurotrophic Tropomyosin-related Kinase (NTRK) 1 fusion sarcoma, but with close radial margins. Repeat tumour board discussion classified her cancer as AJCC Stage III, suggesting repeat surgery for clear margins or alternatively for adjuvant External Beam Radiotherapy and brachytherapy. The patient was keen for repeat surgery.

Unfortunately, a preoperative pelvic MRI in November 2019 showed a new indeterminate T2W hyperintensity at the left vaginal vault, suspicious for recurrent disease. Tumour board discussion advised systemic chemotherapy prior to repeat surgical clearance. Genetic testing, including the NF1 gene, was negative.

The patient completed a total of 3 cycles of Ifosfamide and

Etoposide with brachytherapy. She underwent en-bloc resection of the left pelvic recurrence with left ureter, cuff of posterior bladder and vagina in April 2020. A Boari flap was done and the left ureter was reanastomosed to the bladder. An inadvertent entry into the rectum during dissection was repaired primarily. The patient recovered well post-operatively. The resected specimen showed complete margins. A CT scan of her thorax, abdomen and pelvis in July 2020 showed no evidence of disease recurrence. Thus, her disease-free interval from her third surgery was 3 months and overall survival was 15 months.

#### 3. Discussion

The aggressive nature of MPNST is established in the literature. Reported mortality due to MPNST at 10 years following surgery was as high as 43%, while local recurrence and distant metastasis at 10 years was approximately 30%. Patients with local recurrence were of higher risk for repeated recurrence, distant metastasis and mortality. Other factors affecting prognosis include the presence of NF1, tumour size, and extent of surgical margins (Anghileri et al., 2006). In our case, the aggressive nature of MPNST was characterised by its large size and persistence despite attempts at surgical resection and adjuvant therapy.

While early diagnosis of MPNST is essential, this is challenging from a gynaecological perspective due to its rarity and need for histology confirmation. Typical symptoms of pain may be mistaken for dysmenorrhea while neurological deficits such as weakness or paraesthesia may not be apparent (Gupta et al., 2008). A rapidly growing mass or acute onset of symptoms should trigger suspicions for an aggressive malignant process. This was demonstrated by the rapid regrowth of her endocervical mass less than a year following TCRM and fast local recurrence at the vaginal vault within 3 months after her second completion surgery.

MRI is the gold standard for evaluating nerve sheath tumours of non-gynaecological origin and its intricate anatomical relations (Li et al., 2008). However, MRI may not be reliable in diagnosing MPNSTs as these tumours have well-circumscribed margins and may mimic benign lesions (Sung et al., 2003).

Histopathology is the definitive way to diagnose MPNST. However, there is a lack of specific histological criteria for MPNST (Guellec et al., 2016). MPNSTs are known to demonstrate morphological heterogenicity and variable cellular architecture with no known diagnostic markers for immunohistochemistry (Khin and Cyril, 2014). Our case demonstrated both ovoid and spindle cell types with variable architectural atypia ranging from elongated, small nuclei to scanty pale eosinophilic cytoplasm. Strong positivity for S100 on immunohistochemistry also suggests a nerve sheath origin as it is traditionally regarded as the most sensitive marker for MPNST (Guo et al., 2012). However, there is still limited diagnostic ability as this staining is only seen in 50-60% of MPNST nuclei (Khin and Cyril, 2014). Overall, this presents a diagnostic challenge for MPNST. Thus, it is important to exclude other histological differential diagnoses such as a variety of sarcomas (leiomyosarcoma, rhabdomyosarcoma, dedifferentiated liposarcoma), gastrointestinal stromal tumour or non-mesenchymal tumours (melanoma) (Guellec et al., 2016). In our case, the negative staining for Desmin and Smooth Muscle Actin (SMA) ruled out the possibility of leiomyosarcoma (Monsal et al., 2019:).

Due to the rarity of MPNST in gynaecological patients, the standard of care has not been clearly established. Radical excision of the tumour with clear margins continues to be the mainstay of management (Li et al., 2008; Guo et al., 2012). Chemotherapy may be used to assess patient response whilst tailoring treatment, treating micro-metastases or shrinking tumour for easier surgical resection. Recent trials have suggested MPNST sensitivity to Ifosfamide and Etoposide combinations (Higham et al., 2017). However, MPNST is still generally regarded as chemotherapy insensitive like most soft tissue sarcomas. Thus, its use is generally not for curative intent (Gupta et al., 2008). NTRK directed therapy had not yet been established in our centre, thus was reserved for alternate treatment if necessary.

Radiotherapy demonstrates some benefit in restricting localised disease as well as reducing recurrence rates (Gupta et al., 2008; Khin and Cyril, 2014). It can be used in cases with inadequate surgical resection or local recurrence (Sangiorgio et al., 2018). Nonetheless,

radiotherapy has limited improvement on the long-term survival due to the aggressive nature of MPNST (Gupta et al., 2008).

#### 4. Conclusion

MPNST presenting as a gynaecological tumour is extremely rare. The tumour's aggressive nature and poor prognosis calls for prompt diagnosis, which is challenging due to the lack of histological diagnostic criteria. The recommended treatment is radical surgery with adequate margins. Local recurrences are common and are likely due to the aggressiveness of the tumour. The benefit of chemotherapy and radiotherapy remain uncertain.

#### Informed consent

Informed consent has been obtained from the patient.

#### CRediT authorship contribution statement

Yi Alexander Chuang: Data curation, Writing - original draft. Charissa Goh: Supervision, Writing - review & editing. Chye Lee Kho: Conceptualization, Supervision, Project administration.

#### **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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