

Management of Primitive Neuro-ectodermal Tumor of the Vagina in a Sickle Cell Disease Patient

Zainab A Al-Jufairi, MHPE, FRCOG* Amarjit K Sandhu, MD, FRCOG*
Sara Mathew George, MD, FRCPath**

A twenty-five years old female, a known case of sickle cell disease, presented with frequent and heavy periods of six months duration. Pelvic ultrasound and MRI showed a vaginal mass pushing the bladder anteriorly; the diagnosis of cervical fibroid was considered.

Histopathological examination of the mass revealed a very rare entity of primitive neuro-ectodermal tumor of the vagina. This is the first recorded patient of sickle cell disease with primitive neuro-ectodermal tumor of the vagina. The management was challenging in dealing with her disease and preserving her fertility.

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Primitive neuro-ectodermal tumor (PNET) is rare comprising 1% of soft tissue sarcomas¹. PNET is considered an entity of Ewing's family of tumors. Ewing's family of tumors is not a single condition but a group of closely related tumors². These tumors have a similar natural history, prognosis, immunohistochemical and cytogenetic profiles³. These tumors are defined as round cell sarcoma that shows varying degree of neuro-ectodermal differentiation⁴. Primitive neuro-ectodermal tumors can be classified into central and peripheral PNETs according to the cells of origin. Central PNETs originate from the neural tube, which includes the brain and spinal cord, while peripheral PNETs arise from the neural crest, which includes sympathetic nervous system, bones or soft tissues⁴.

The most common site of PNET is chest and it is known as Askin tumor. PNET was reported in the head, neck, kidney and lungs⁵⁻⁷. However, PNET of the female genital tract are rare, occurring in the ovaries, uterus, cervix, vagina and vulva³. Presentation in the vagina is exceedingly rare⁸⁻¹⁵. PNET tumors occur more commonly in the second decade of life. It affects mainly Whites and Hispanics and to a less extent African and Asians⁵.

To our knowledge, this is the first patient with sickle cell disease who presented with PNET of the vagina. The management of the patient was demanding because of her age, sickle cell disease and the need to preserve her fertility.

* Consultant Obstetrician and Gynecologist

** Consultant Pathologist

Salmaniya Medical Complex

Kingdom of Bahrain

Email: mamoamen@batelco.com.bh

The aim of this report is to present a rare case of neuro-ectodermal tumor of the vagina in a patient suffering sickle cell disease.

THE CASE

A twenty-five-year-old woman suffering from sickle cell disease presented to the gynecology clinic with history of prolonged vaginal bleeding, secondary dysmenorrhoea and frequency of micturition of six months duration. On examination, there was mild pallor with no jaundice and no lymphadenopathy. Cardiovascular and respiratory examinations were normal. The abdomen was soft with no organomegaly and the uterus was not palpable. Vaginal examination was not performed because of virginity.

Investigation revealed that her hemoglobin was 9.9 g/dl and platelet count was $141 \times 10^9/l$. Pelvic and abdominal ultrasound showed a normal anteverted uterus with normal endometrial thickness. There was a heterogeneous solid mass containing some tiny cystic areas arising inferior and to midline of the cervix at the level of the vagina. The mass measured 8x8x7 cm with moderate internal vascularity. The lesion appeared to be separate from the uterus and the cervix. The impression was that it could be pedunculated cervical fibroid; however, the possibility of vaginal tumor could not be excluded. There was moderate splenomegaly and the kidneys looked normal with no hydronephrosis. MRI of the pelvis demonstrated a large heterogeneous pelvic mass displacing the cervix superiorly and indenting the urinary bladder. The outline of the uterus appeared normal with normal endometrial strip (Figure 1). There were no adnexal masses or pelvic lymphadenopathy. A diagnosis of pedunculated cervical fibroid was made. Intravenous pyelography did not reveal any structural abnormality.

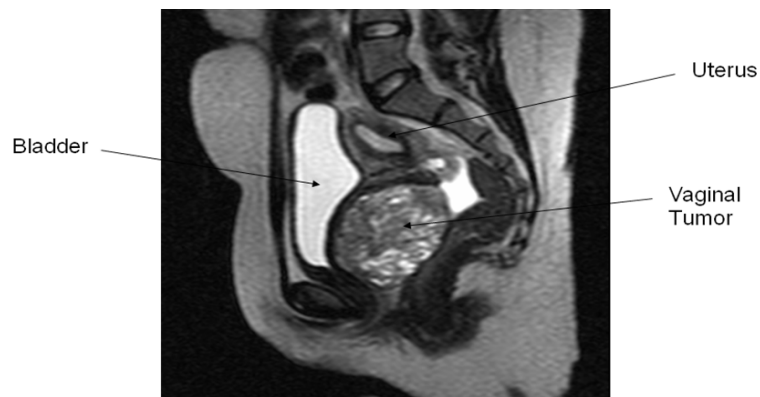


Figure 1: MRI Sagittal View Showing Large Vaginal Tumor Displacing the Bladder Anteriorly and the Uterus Superiorly

This patient was admitted for cystoscopy, ureteric catheterization, laparotomy and myomectomy. The patient and her relatives were counseled regarding examination under anesthesia because she preferred not have vaginal examination unless it is mandatory. We explained to them the possibility of hysterectomy if life threatening uncontrolled haemorrhage

occurred. Cross matching of four units of packed cells was performed with great difficulty as she had allo-antibodies due to previous blood transfusion.

A combined team of urologists and gynecologists performed the surgery. Cystoscopy showed a clear view of the bladder and the trigone was pushed anteriorly by the pelvic mass. Ureteric orifices could not be visualized, so it was difficult to perform ureteric catheterization. The abdomen was opened by midline vertical incision. Intra-operatively, the uterus, cervix, fallopian tubes and ovaries were normal. The mass was not visible; the utero-vesical fold was opened and the bladder was pushed as far as the vaginal mass was palpable. A transverse incision on the anterior vaginal wall was made and the mass was identified. A smooth lining mass was arising from the postero-lateral wall of the vagina. As soon as we opened the mass, necrotic tissue was drained. Deroofing of the mass was performed as we thought it was very dangerous to excise the mass as a whole because of the possibility of ureteric and/or bladder injuries. The vaginal wall closed and hemostasis was achieved. Intra-operative blood loss was about 400 ml and she required blood transfusion on her second postoperative day. Her postoperative period was uneventful and was discharged on the seventh day.

Histopathological examination showed a malignant small blue round cell tumor with perivascular arrangement, areas of necrosis and hemorrhage and PAS positivity in the cells indicating the presence of intracytoplasmic glycogen (figure 2, 3, 4, 5). The light microscopic diagnosis of primitive neuro-ectodermal tumor of the vagina was supported by immunohistochemical (IH) studies. The tumor was positive for vimentin, NSE, synaptophysin and CD 99 (figure 6). Other IH markers such as Desmin, myoD1, MNF 116 (cytokeratin), Leukocyte Common Antigen and Muscle Specific Actin were negative.

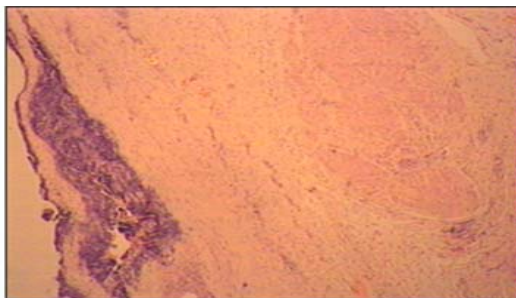


Figure 2: Photomicrograph of Vaginal Wall with Neoplastic Cells in the Deeper Part (H & E Stain, 400 x Magnification)

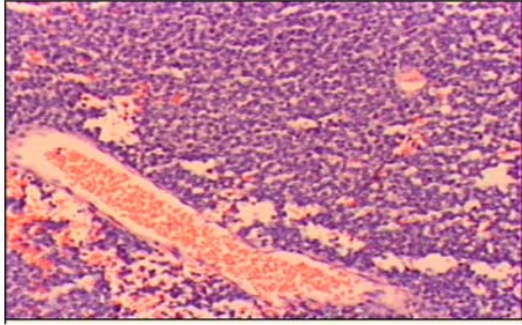


Figure 3: Photomicrograph of Neoplastic Cells Showing Perivascular Arrangement (H & E Stain, 100 x Magnification)

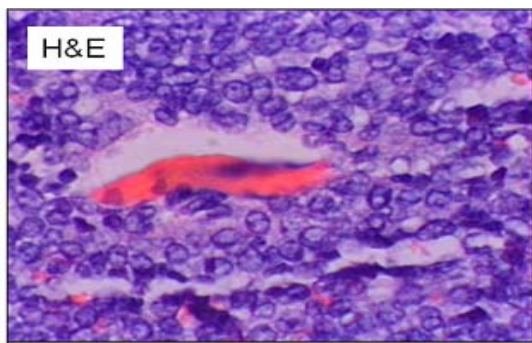


Figure 4: Photomicrograph of the Small Blue, Round Neoplastic Cells (H & E Stain, 400 x Magnification)

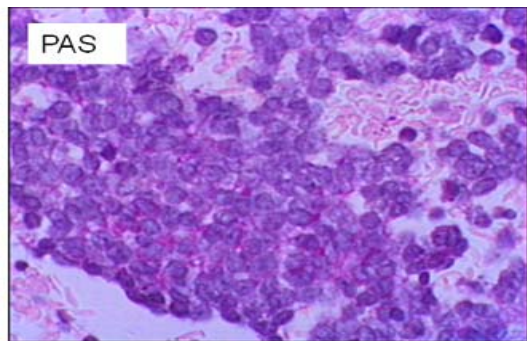


Figure 5: Photomicrograph of the Neoplastic Cells Stained Positive with PAS Stain (400 x Magnification)

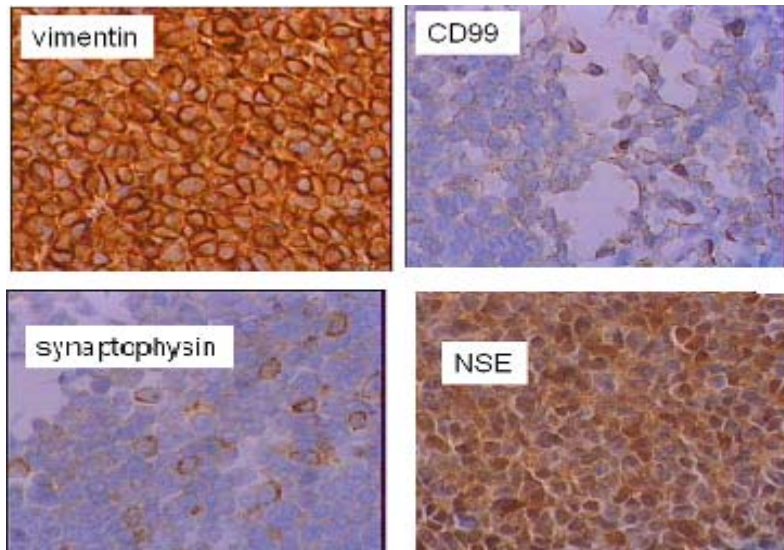


Figure 6: Photomicrograph of the Neoplastic Cells Stained Positive with Immunohistochemical Marker of Vimentin, CD99, Synaptophysin and NSE (400 x Magnification)

She was referred to the oncology department where she received 6 cycles of chemotherapy (vincristine, adriamycin, cyclophosphamide VAC alternating with etoposide and ifosfamide) and later six cycles of intracavitary vaginal brachytherapy. She tolerated the treatment and got married during her treatment. She was free of the disease at the time of writing this report one year following the surgery.

DISCUSSION

PNET of the vagina presents usually as a rapidly growing painful deep mass. Some patients can present with watery and foul smelling discharge per vagina and pressure symptoms such as tenesmus and difficulty in passing urine³. The age of previously seven reported cases of PNET of the vagina varied between 17 and 47 years old. The size varies from 3 to 10 cm in less than one year⁹⁻¹⁵.

The neoplasm has a lobulated architecture and composed of solid aggregates of cells¹⁴. It is a small round cell tumor with variable degree of neural, glial, ependymal and medulloepithelial differentiation containing well-formed rosettes³. The tumor is composed of solid sheets of undifferentiated small round cells with numerous Homer-Wright rosettes^{3,7-13}. Immunohistochemical studies help in differentiating PNET from other round cell pathologies³.

Positivity for CD 99, a product of MIC2 gene on the X chromosome, is useful in confirming the diagnosis but it is not specific^{3,9-14}. MIC2 was found to be positive in T lymphoblastic lymphoma, poorly differentiated synovial sarcoma, some neuro-endocrine carcinomas and rare cases of rhabdomyosarcoma⁹. Vimentin was also reported to be positive in several patients with PNET of the vagina^{9,10,13,14}. Other immunohistochemical (IH) markers such as Fli-1 protein, synaptophysin, neuron-specific enolase and S 100 protein were also found to be positive in

PNET of the vagina^{1,9,13,14}. Lack of desmin, myogenin and myoD1 can rule out rhabdomyosarcoma and LCA negativity excludes lymphoma⁹.

In our patient, the tumor was positive for vimentin, NSE, synaptophysin and CD 99 (figure 6). Other IH markers such as Desmin, myoD1, MNF 116, LCA and MS. ACTIN were negative.

Ewing's sarcoma and primitive neuroectodermal tumor share a specific t (11; 22) (q24;q12) chromosomal translocation. The breakpoints involve the EWS gene on chromosome 22 and the FLI-1 gene on chromosome 11. The sensitivity of reverse transcription polymerase chain reaction by using oligonucleotide primers derived from EWS and FLI-1 complementary DNAs approaches 87% as compared to 30-50% in ordinary karyotyping^{9,16}. Several cases of vaginal PNET were found to have EWS and FLI-1 genes by molecular study^{9,14}.

Surgery, chemotherapy and radiotherapy is the treatment of PNET of the vagina³. It varies from tumor biopsy, wide local excision of the tumor and radical surgery consisting of wide local excision and abdominal hysterectomy with bilateral salpingo-oophorectomy^{3,7,12,13}. The chemotherapy used in the treatment of PNET of the vagina is similar to high-risk protocol for Ewing's family of tumors³. This chemotherapy protocol consists of high-dose intermittent multi-agent chemotherapy (vincristine, cyclophosphamide, adriamycin [doxorubicin] alternating with ifosfamide and etoposide) for 6 cycles^{1,17-19}. As this tumor is highly aggressive, combination chemotherapy for 70 weeks following local therapy, with surgery or radiotherapy, is needed³.

Adjuvant radiotherapy is used in the treatment of PNET of the vagina. This consists of intracavitary brachytherapy and external radiation of the pelvis for the inoperable tumors^{11,12}.

The management of our patient was very challenging because she was young and suffering from sickle cell disease. She was managed by gynecologist, urologist, hematologist, oncologist and radiotherapist. She tolerated the multi-agent chemotherapy in spite of her sickle cell disease. This patient was reluctant to start intra-cavitary brachytherapy because she got married during the follow-up period and was scared from the ill effect of radiation on her reproductive system. She was counseled about ovarian suspension and frozen embryos but finally she accepted radiotherapy.

Progress in the treatment of Ewing's sarcoma has improved the survival rate from 10% to 75% after the introduction of chemotherapy for patients with localized tumors¹⁷. PNETs arising from extra osseous sites have an aggressive history and poor prognosis compared to Osseous PNETs²⁰. However, literature review has shown PNETs of the vagina have relatively favorable outcome similar to the vulvar and non-gynecological cutaneous ES-PNET^{3,13}. Women with vaginal PNET were reported to be free from the disease 18 to 48 months of follow-up¹⁰⁻¹³.

CONCLUSION

This case describes a rare site of primary Ewing's sarcoma/PNET. Management of these patients involves multidisciplinary approach to improve the outcome and survival rate. This patient demonstrates the need for conservative management in young women to preserve the fertility.

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