Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medical Oncology

Successful Management of Locally Advanced Primitive Neuroectodermal Tumor (PNET) of the Urinary Bladder: a Case Report and Literature Review

M.A.Mokhlis[1*], L.Alaoui[1], A.Maghouss[3], M.Allaoui[2], C.el M'hadi[1], M.R.Khmamouch[1], T.Mahfoud[1], K.Alaoui Slimani[1], H.Sifat[3], R.tanz[1], M.Ichou[1]

[1]Department of Medical Oncology, Military Hospital of Instruction Mohamed V, Morocco
[2]Anatomopathology Laboratory, Military Hospital of Instruction Mohamed V, Morocco
[3]Radiotherapy Department, Military Hospital of Instruction Mohamed V, Morocco

DOI: 10.36347/sjams.2022.v10i02.011 | **Received:** 02.01.2022 | **Accepted:** 08.02.2022 | **Published:** 13.02.2022

***Corresponding author:** M.A. Mokhlis
Department of Medical Oncology, Military Hospital of Instruction Mohamed V, Morocco

Abstract **Case Report**

Background: Primitive neuroectodermal tumors (PNETs) are highly malignant neoplasms arise from neuroectodermal cells that have cholinergic features. These tumours are closely related to osseous or extraosseous Ewing's sarcomas, with which they share the same chromosomal abnormality. Over the last few years, PNETs have been increasingly reported to occur in various organs, which may be due to recent progress in immunohistochemical techniques. PNETs arising in the urinary bladder are extremely rare, but more frequent in older adults. ***Case presentation***: A 16 years Moroccan men old, who consults for a total hematuria and dysuria evolving for 2 months in a context of deterioration of the general state. Cyst biopsy was performed. The morphological result in favor of an undifferentiated round cell tumor process infiltrating the bladder muscle, the immu-histochemical study was in favor of a round cell tumor of the Ewing sarcoma/PNET type. Pelvic Magnetic resonance imaging MRI revealed the presence of an endovesical process invading the left antero-inferior pre-vesical fat. We decided, after a multidisciplinary consultation meeting, to start with two cycles of neoadjuvant chemotherapy, then to propose locoregional treatment, either radiotherapy or partial resection. The patient was put on the VAC/IE protocol with a clear regression in tumor size after two cycles. ***Conclusion:*** Both clinician and pathologist must be aware of this rare entity during diagnosis and management. Surgery or radiotherapy supported with chemotherapy should be considered an option, especially in advanced disease. Studies of more cases of primary PNET of the urinary bladder with longer follow-up periods are needed to clarify the clinical features and treatment.

Key words: PNET, ewing's sarcomas, bladder, VAC/IE.

INTRODUCTION

Primitive neuroectodermal tumors (PNETs) was first described in 1918 and comprises a group of small, round-cell tumors characterized by neuroectodermal differentiation that occurs predominantly in the bones and soft tissue of children and young adults [1]. These highly malignant neoplasms arise from neuroectodermal cells that have cholinergic features. These tumors are closely related to osseous or extra osseous Ewing's sarcomas, with which they share the same chromosomal abnormality: t (11; 22) (q12; q24) [2], and, in fact, both are considered to be members of the Ewing family of tumors. The peak incidence of PNET is at ages from 10 to 20 years [3]. The majority of cases present in the soft tissues and less frequently in the skeletal system. Over the last few years, PNETs have been increasingly reported to occur in various organs, which may be due to recent progress in immunohistochemically techniques. PNETs arising in the urinary bladder are extremely rare, but more frequent in older adults. Most of the patients in the only 18 reported cases identified in the medical literature were at a late stage when diagnosed with the disease, and the tumor had already infiltrated the muscle or metastasized, leading to poor prognosis [4-7]. Here, we report a case of a newly diagnosed symptomatic advanced bladder tumor. The complete clinical, pathological, and follow-up data of the patient were used to confirm PNET of the urinary bladder.

CASE REPORT

A 16-year-old Moroccan man with no significant history of personal illness or family cancer, who consults for a total hematuria and dysuria evolving

for 2 months in a context of deterioration of the general state. An emergency indwelling balloon urethral catheter was inserted due to acute urinary retention. During initial admission, cystoscopy revealed a great smooth, rounded, soft-tissue mass, which takes up almost the entire anterior wall of the bladder. Cyst biopsy was performed. the morphological result in favor of an undifferentiated round cell tumor process infiltrating the bladder muscle, the immuno-histochemical study was in favor of a round cell tumor of the Ewing sarcoma/PNET type (antibody anti-CD99, anti-NSE and anti-PS100 antibodies were positive, However, they were negative for cytokeratin 8, cytokeratin 18, cytokeratin 20, and epithelial membrane antigen) **(fig 1).** Pelvic Magnetic resonance imaging MRI revealed the presence of an endovesical process, measuring 9.3 x 8.4 cm extended over 11.3 cm heterogeneous in T2, which is heterogeneously enhanced after injection of gadolinium. This process invades the left antero-inferior pre-vesical fat in front, and is responsible for bilateral uterus-hydro-nephrosis behind. No abnormal pelvic lymph nodes were observed **(Fig. 2).** Thoraco-abdomino-pelvic Computed Tomography and FDG-PET scan detected no distant visceral organs or bones metastases. Then, the patient is transferred to us for care. Physical examination of patient shows clinical anemic syndrome with persistent hematuria, with stable hemodynamic status. The patient's weight was 65kg and height was 182cm. The biological assessment shows a normochromic normocytic anemia at 7g/dl requiring a blood transfusion and the placement of a double current urinary catheter. Routine other blood and biochemical indexes were normal.

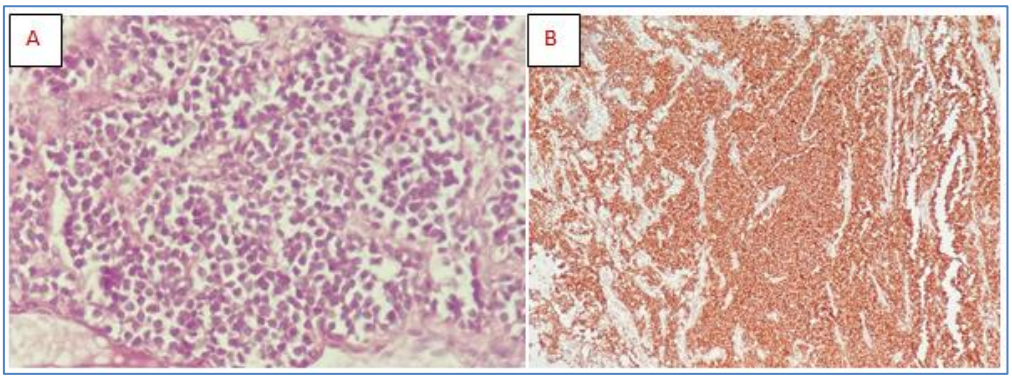

Fig-1: A= Round cell tumor proliferation (HE, Gx400), B= strong and diffuse membrane labeling of the anti CD99 antibody

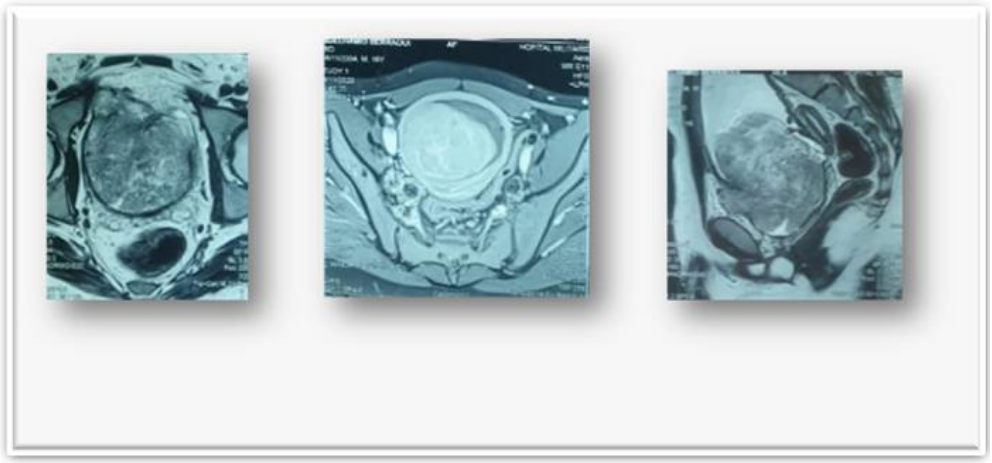

Fig-2: Different sequences of the initial pelvic MRI showing a process invading the left antero-inferior pre-vesical fat in front, and is responsible for bilateral uterus-hydro-nephrosis behind

We decided, after a multidisciplinary consultation meeting, to start with two cycles of neoadjuvant chemotherapy, then to propose locoregional treatment, either radiotherapy or partial resection (cystoprostatectomy is refused by the patient taking into account the infertility caused by the surgery). The patient was put on the VAC/IE protocol (VAC= Vincristine 2 mg/m2 (maximum dose of 2 mg) IV once on day 1, Doxorubicin 75 mg/m2 IV bolus once on day 1, Stop once cumulative dose received by the patient exceeds 375 mg/m2 and switch to Dactinomycin 1.25 mg/m2 IV once on day 1, Cyclophosphamide 1200 mg/m2 IV once on day 1 with Mesna after Cyclophosphamide for prevention of hemorrhagic cystitis / IE at day 15= Ifosfamide 1800 mg/m2 IV once per day on days 1 to 5 with Mesna, Etoposide 100 mg/m2 IV once per day on days 1 to 5). The clinical evaluation after one single cycle shows the disappearance of all the urinary disorders and the definitive removal of the catheter was recommended.

Pelvic MRI performed after two cycles shows a clear regression in size estimated at 70% (a mass which measures only 34x34X34mm) **(fig 3).** Transurethral resection of the bladder tumor (TURBT) was performed, twice, and both times the resection was incomplete leaving macroscopic lesions. The decision was to do radiotherapy at a curative dose for 25 sessions then complete a year of the same VAC/IE protocol.

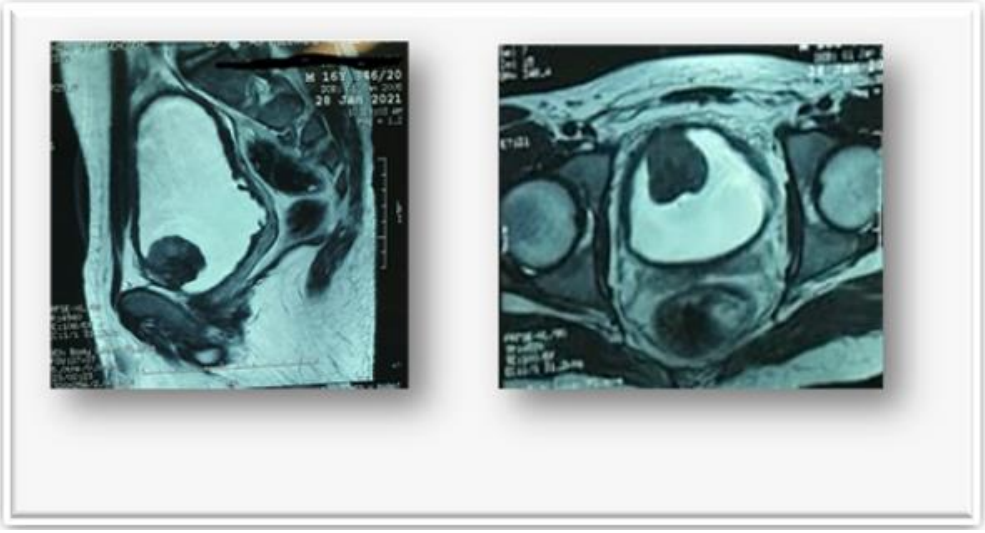

Fig-3: Pelvic MRI control after two cycles of VAC/IE chemotherapy protocol showing a clear regression in size estimated at 70% (a mass that measures only 34x34X34mm)

DISCUSSION

Primitive neuroectodermal tumor of the urinary bladder is a distinct high-grade malignant neoplasm belonging to the Ewing family of tumors. It represent a rare entity due to the very small number of reported cases. The review of the literature [8-13] show that the age of patients with primary ES/PNET in the urinary bladder including our patient ranged from 10 to 81, with a mean age of 44. Hematuria was the most frequent presenting symptom. Additionally, some patients presented with bilateral hydronephrosis, renal failure and edema in lower extremities, which were associated with advanced disease. There was no gender tendency, with eight female and eight male patients. Intravenous pyelography, magnetic resonance imaging, ultrasonography, computed tomography and bone scintigraphy were used as imaging studies at the diagnosis and patient evaluation. Five cases were metastatic at the time of diagnosis and 2 tumors had perivesical infiltration. Immunodeficiency has been reported as a risk factor for Ewing family tumors, similarly, in this population, five patients were immune-suppressed: one due to renal transplantation, one due to chemotherapy for squamous cell carcinoma of bladder, one due to Hodgkin's disease, one due to ALL (acute lymphoblastic leukemia), and one due to chemotherapy for another malignancy; this may confirm immunodeficiency as a risk factor. As a result, the relationship between immunodeficiency and PNET of the bladder and the precise pathogenesis were still not explicit, and hence, larger-sample studies on this association are needed to further expound the specific underlying mechanism accurately. Advanced age, metastatic disease and limited resection may be related to poor prognosis.

To confirm diagnosis, immune-histochemical and/or molecular analysis are necessary in addition to histology. In this patient, there was strong immunoreactivity for the CD99 antigen. Reactivity to vimentin, and S-100 may suggest diagnosis but are not pathognomonic. Generally, Light microscopy showed a glycogen-rich, small round cell tumour without rosettes or intercellular fibrillar material, which virtually excluded neuroblastoma. Ultrastructural study was useful in our case, showing occasional dense-core granules with complex cytoplasmic processes, which are common in PNETs [14, 15]. Tumour cells expressed CD99, vimentin, cytokeratin and S-100 protein, a profile highly suggestive of PNET. Although not specific for PNET or Ewing's sarcoma, CD99 is usually present in these tumors [16]. It must be used with antibodies to vimentin, seen in most cases of PNET, or cytokeratin stain, as reported in our case, in up to 57% of soft tissue samples. Neurone-specific enolase, S-100 protein, neurofilaments and other neural markers showed a variable degree of expression in reported cases. Moreover, the lack of staining of muscle, lymphoid or neuroendocrine markers virtually excludes rhabdomyosarcoma, haematolymphoid neoplasm or neuroendocrine carcinoma [17].

Molecular analysis supports the final decision of ES/PNET by showing the EWS gene rearrangement via FISH, and the reciprocal translocation t (11; 22) (q24; q12) and EWS/FLI-1 fusion transcript via RT-PCR. This typical translocation is found in 85% of cases **[18].** The EWS gene rearrangement is seen also in

desmoplastic small round cell tumor (DSRCT); however, its fusion partner in DSRCT is the WT-1 gene, not FLI-1. In fact, differentiating DSRCT from ES/PNET can be challenging at times because of the overlapping morphologic features. Nevertheless, immunohistochemistry will resolve the issue in most cases, as DSRCT will show nuclear WT-1 staining as well as paranuclear dotlike cytokeratin and/or desmin expression.

Because of the small number of patients with PNET, It has not been possible to establish definitive guidelines regarding its management and treatment. Given its close relation with Ewing's sarcoma, radical resection, adjuvant radiation, and multiregimen chemotherapy are the recommended therapeutic modalities. Aggressive surgery is still the main comprehensive therapeutic method of the bladder. Aggressive surgery combined with adjuvant chemotherapy may extend the survival more considerably compared with the administration of only TURBT and chemotherapy. Whether TURBT of PNET of the bladder is an effective therapy is unclear.

When treated with local control measures only (surgery or radiation therapy), the disease has a high mortality rate. Doxorubicin-based chemotherapy regimens including cyclophosphamide, vincristine and dactinomycin have been associated with improved outcomes [19]. The addition of iphosphamide and etoposide to the standard regimen can also improve outcomes for non-metastatic Ewing's sarcomas/ PNET, but this is not effective in the case of metastatic disease [20]. Grier et al. published data from a randomized trial showing that the addition of ifosfamide and etoposide (IE) to a standard regimen of vincristine, doxorubicin, and cyclophosphamide (VAC) significantly improved the outcome for patients with non-metastatic Ewing sarcoma, primitive neuro-ectodermal tumor of bone, or primitive sarcoma of bone. More recently, however, dose intensive neo-adjuvant chemotherapy followed by local treatment has been favored because of improved results by the addition of systemic therapy. Our case was a 16-year-old male with no comorbidities and risk factors. He had a locally advanced disease at the time of diagnosis, he had no distant metastases, and no symptoms due to advanced disease the young character of the patient and his desire for fertility could not retain the indication of oncological surgery, namely a radical cysto-prostatectomy. Although the response of sarcomas to high dose radiotherapy is well defined, its use in ES/PNET of the bladder has not been well established yet, but it was the only feasible option.

CONCLUSION

Both clinician and pathologist must be aware of this rare entity during diagnosis and management. Surgery or radiotherapy supported with chemotherapy should be considered an option, especially in advanced disease. Studies of more cases of primary PNET of the urinary bladder with longer follow-up periods are needed to clarify the clinical features and treatment.

REFERENCES

1. Stout, A.P. (1918). A tumor of the ulnar nerve. Proc NY Pathol Soc 18: 2–12
2. Amiel, A., Ohali, A., Fejgin, M., Sardos-Albertini, F., Bouaron, N., Cohen, I. J., & Avigad, S. (2003). Molecular cytogenetic parameters in Ewing sarcoma. *Cancer genetics and Cytogenetics*, *140*(2), 107-112.
3. Scurr, M., & Judson, I. (2006). How to treat the Ewing's family of sarcomas in adult patients. *The oncologist*, *11*(1), 65-72.
4. Banerjee, S. S., Eyden, B. P., McVey, R. J., Bryden, A. A. G., & Clarke, N. W. (1997). Primary peripheral primitive neuroectodermal tumour of urinary bladder. *Histopathology*, *30*(5), 486-490.
5. Colecchia, M., Dagrada, G. P., Poliani, P. L., & Pilotti, S. (2002). Immunophenotypic and genotypic analysis of a case of primary peripheral primitive neuroectodermal tumour (pPNET) of the urinary bladder. *Histopathology*, *40*(1), 108-109.
6. Desai, S. (1999). Primary peripheral primitive tumour of urinary bladder. Histopathology 32: 477–478
7. Mentzel, T., Flaschka, J., Mentzel, H. J., Eschholz, G., & Katenkamp, D. (1998). Primary primitive neuroectodermal tumor of the urinary bladder. Clinicopathologic case report and differential small cell tumor diagnosis of this site. *Der Pathologe*, *19*(2), 154-158.
8. Busato, W. F., Almeida, G. L., & Ogata, D. C. (2011). Primary primitive neuroectodermal tumor of the bladder: histologic and clinical features of 9 cases. *Clinical Genitourinary Cancer*, *9*(1), 63-67.
9. Osone, S., Hosoi, H., Tanaka, K., Tsuchiya, K., Iehara, T., Morimoto, A., ... & Sugimoto, T. (2007). A case of a Ewing sarcoma family tumor in the urinary bladder after treatment for acute lymphoblastic leukemia. *Journal of Pediatric Hematology/Oncology*, *29*(12), 841-844.
10. Al Meshaan, M. K., Nayef, M., Kwaider, T., Otto, W., & Katchy, K. C. (2009). Peripheral primitive neuroectodermal tumor of the urinary bladder in an Arab woman with history of squamous cell carcinoma: a case report. *Journal of Medical Case Reports*, *3*(1), 1-4.
11. Nawal Rao, R., Sinha, S., Babu, S., & Mehrotra, R. (2011). Fine-needle aspiration cytology of primitive neuroectodermal tumor of the urinary bladder: A case report. *Diagnostic Cytopathology*, *39*(12), 924-926.
12. Okada, Y., Kamata, S., Akashi, T., Kurata, M., Nakamura, T., & Kihara, K. (2011). Primitive neuroectodermal tumor/Ewing's sarcoma of the urinary bladder: a case report and its molecular diagnosis. *International journal of clinical oncology*, *16*(4), 435-438.

13. Zheng, Y., Tan, F., Wang, L., Xu, N., & Mou, H. (2011). Primary primitive neuroectodermal tumor of the urinary bladder: a case report and literature review. *Medical Oncology*, *28*(1), 388-391.
14. Mentzel, T., Flaschka, J., Mentzel, H. J., Eschholz, G., & Katenkamp, D. (1998). Primary primitive neuroectodermal tumor of the urinary bladder. Clinicopathologic case report and differential small cell tumor diagnosis of this site. *Der Pathologe*, *19*(2), 154-158.
15. Banerjee, S. S., Eyden, B. P., McVey, R. J., Bryden, A. A. G., & Clarke, N. W. (1997). Primary peripheral primitive neuroectodermal tumour of urinary bladder. *Histopathology*, *30*(5), 486-490.
16. De Alava, E., Kawai, A., Healey, J. H., Fligman, I., Meyers, P. A., Huvos, A. G., ... & Ladanyi, M. (1998). EWS-FLI1 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma. *Journal of Clinical Oncology*, *16*(4), 1248-1255.
17. Cheng, L., Pan, C. X., Yang, X. J., Lopez-Beltran, A., MacLennan, G. T., Lin, H., ... & Eble, J. N. (2004). Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 64 patients. *Cancer*, *101*(5), 957-962.
18. Aurias, A., Rimbaut, C., Buffe, D., Dubousset, J., Mazabraud, A. (1983). Chromosomal translocations in Ewing's sarcoma. *N Engl J Med, 309*:496-7
19. Nesbit, M. E., Perez, C. A., Tefft, M., Burgert, E. O., Vietti, T. J., Kissane, J., ... & Gehan, E. A. (1981). Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: an Intergroup Study. *Natl Cancer Inst Monogr*, *56*, 255-262.
20. Grier, H. E., Krailo, M. D., Tarbell, N. J., Link, M. P., Fryer, C. J., Pritchard, D. J., ... & Miser, J. S. (2003). Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *New England Journal of Medicine*, *348*(8), 694-701.