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Histopathology

PRIMITIVE NEUROECTODERMAL TUMOUR – CASE REPORT IN 3 YEAR OLD MALE AND SUMMARY OF FEATURES, CATEGORIZATION AND MANAGEMENT OF DISEASE

Dr Kahkashan Riaz	Assitant Professor, Department of Pathology, Velammal Medical College and Research institute
Dr Ziauddin	Senior Resident, Department of Urology, Meenakshi Mission hospital and Research center
Dr Prabha Verma	Assitant Professor, Department of Radiation oncology, KMC hospital, Meerut
Dr Harshita Baranwal	Assitant Professor, Department of Pathology, Government Medical College, Orai
Dr Pinky	Senior Resident, Department of Pathology, Velammal Medical College and Research institute

ABSTRACT Extraosseous Ewing's sarcoma/primitive neuroectodermal tumors (ES/PNET) are a relatively rare group of malignant tumors that occur in children and adolescents aged between 10–20 years. ES/PNET are highly aggressive and generally show poor prognosis because of the lack of clear clinical symptoms during the early stages. These tumors mainly occurs in the extremities and retroperitoneum, and are seldom in the internal organs. ES/PNET of the bladder is rare, with only a few reports available at present. We report a case of primary PNET of the bladder that occurred in a 3-year-old male and also summarise the clinical features, categorization and management of the disease.

KEYWORDS : Ewing like sarcoma, aggressive, immunohistochemistry, chemotherapy, poor prognosis

INTRODUCTION

Both Ewing and Ewing-like sarcoma are aggressive tumors characterized by the presence of neoplastic, round mesenchymal cells, which are most frequent in children and young adults.[1] Ewing-like tumors represent a morphologically and molecularly heterogeneous group of neoplasms that are histologically similar to Ewing sarcoma but without the presence of canonical fusions between the EWSR1 gene and members of the ETS family of transcription factors.[1] Three main types of Ewing sarcomas have been described: bone, extraosseous, and primitive neuroectodermal tumors (PNET). [2]

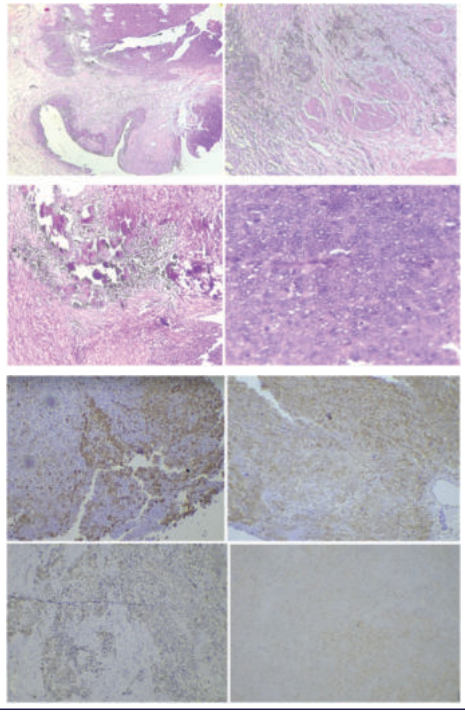
Incidence of these tumors' peaks in children and young people aged 10–20 years, with an incidence of 3 cases per million under the age of 20.[3] On the other hand, bladder PNET are extremely rare but are most frequent in older adults.[4] ES/PNET are highly aggressive and generally portend poor prognosis [6] because of the lack of clear clinical symptoms during the early stages. These tumors frequently occur in the extremities and retroperitoneum [7,8] and are seldom in the internal organs. Just 19 cases of bladder PNET have been described in the literature, and most were diagnosed at advanced stages, when the tumor was invasive or metastatic, resulting in a poor prognosis. This study presents a case of Ewing sarcoma/primary bladder PNET in 3 year old boy at the time of diagnosis. We will further summarize the clinical features, histological and the therapeutic options for this aggressive disease.

Case Report

A 3-year-old boy presented to the surgery department (ED) in a tertiary center of South India, complaining of hematuria and dysuria for the previous 24 h and pain in the right renal fossa over the previous two weeks. The patient had an acute deterioration of the kidney function, with creatinine (Cr) levels of 0.4 mg/dl, hence a scan was performed. Abdominopelvic computed tomography (CT) scan without contrast revealed right hydroureteronephrosis, secondary to a bladder lesion on the right posterolateral wall. A transurethral resection of the bladder was scheduled. The anatomopathological study showed parietal invasion (including the muscular layer) by a malignant tumour, which presented a dense proliferation of small, round basophils, with scant cytoplasm and hyperchromatic, rounded nuclei. It was reported as malignant small round cell tumour.

A more detailed immunohistochemical study was then required, with the rest of the biomarkers assessed also showing negative results: (excluding poorly differentiated carcinoma); chromogranin and synaptophysin (excluding a neuroendocrine tumor). Immuno histochemistry favours poorly differentiated small round cell tumour. Patient was referred to radiation oncology department. Hence, the patient received systemic treatment with chemotherapy schedule consisting on vincristine, doxorubicin , cyclophosphamide + mesna (detoxifying agent) for 21 days. Prior to the fourth chemotherapy cycle, a PET-CT control scan showed a partial response to treatment. Further patient went to other hospital and loss to follow up.

An abdominopelvic CT without contrast revealed right hydro ureteronephrosis, prompting an emergency urinary diversion through a right percutaneous nephrostomy. Despite the urinary diversion, the patient's general condition further deteriorated, with no improvement in kidney function along with worsening hydroelectrolytic alterations that led to a hypocalcemic state. Ionic and antibiotic corrective measures could not prevent multiorgan failure, which ended in the patient's death.



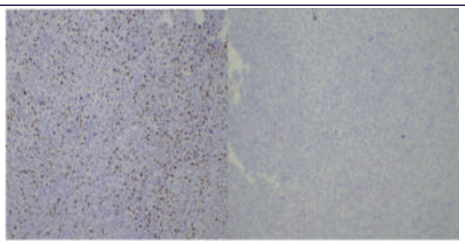


Figure 1: Bladder tissue infiltrated by monomorphic large sized, atypical cells separated by thin fibrous septa. [H&E stain, x100]; **Figure 2:** Muscle invasion by atypical cells was seen[H&E stain, x100]; **Figure 3:** Foci of calcification and necrosis are also seen; **Figure 4:** Atypical cells displaying round to oval nuclei with irregular nuclear contours, prominent nucleoli and small amount of cytoplasm. Brisk mitotic activity(3-5 hpf) is noted. [H&E stain, x400]; **Figure 5:** Immunohistochemistry for SMA positive in myoid areas[H&E stain, x100]; **Figure 6:** I mmunohistochemistry shows CD99 positive[H&E stain, x100]; **Figure 7:** Immunohistochemistry shows CD56 positive [H&E stain, x100]; **Figure 8** Immunohistochemistry for synapto physin positive[H&E stain, x100]; **Figure 9:** Ki 67 proliferation index~40%[H&E,x100];Figure 10:Immunohistochemistry for S100,DESMIN,MYOGENIN,FL-1,CD45,CD34,PANCK&WT-1:Negative [H&E stain, x100]

DISCUSSION

Because bladder PNET is a very rare cancer, no definitive management or treatment guidelines have been established. This extremely aggressive, malignant tumor originates in the migratory embryonic cells of the neural crest, appearing predominantly in adults.[3] To date, just 19 cases of bladder PNET have been described in the literature, so most information on its management has been gleaned from experience with Ewing sarcoma. Molecular tests with fluorescent in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR) have shown an EWS/FLI-1 gene fusion in some patients with PNET.[4] Regarding the clinical presentation, hematuria is the most frequent symptom, followed by dysuria, increased frequency of urination, and hydronephrosis. There were no differences between sexes, with 8 published cases in men and 11 in women. The protein resulting from this fusion, generated by the translocation of t (11; 22) (q24; q12), may be one pathogenic factor in the development of a PNET.[5] Based on the cases of bladder PNET reported to date, it appears that advanced age, metastasis, and incomplete tumor resection are determinants of a poor prognosis.

In general, tumors grade and classification are the fundamental basis for neuroendocrine tumors (NETs) therapeutic decisions[9]. Tumor grade is a system used to predict how fast tumors would grow/spread and differentiation is a key feature to predict their behavior[10]. Ki-67 (MIB1) only stains actively dividing cells and not resting cells, is most commonly used to establish the grade of the tumor; thus, more dividing cells implies more aggressive PNETs. The world health organization classifies PNETs into three main categories based on the Ki67 proliferation index and/or mitotic count per 10 high power fields. Well-differentiated PNETs (also known as panNETs) are classified as Grade 1 (low grade), Grade 2 (intermediate grade), and Grade 3 (high grade) with a Ki67 index of < 2%, 2%-20%, and > 20% respectively. Poorly differentiated PNETs (also referred to as panNEC) are categorized as grade 3 (high grade) with a Ki67 index greater than 20%[11]. Also, tumor grade strongly predicts outcomes such as how fast the tumor will grow and how long it can be controlled with therapy. For well-differentiated grade 1, meaning PNETs patients who have small low-grade tumors, oncologists often wait and do not operate (watchful waiting protocol) and most recently treat with the PRRT (Peptide receptor radionuclide therapy), a treatment that is well tolerated and very safe [12]. Well-differentiated grade 3 PNETs are fairly indolent but often have an unpredictable course and behave similarly to grade 2 panNETs; poorly differentiated grade 3 panNEC are aggressive[13].

Consequently, relevant studies are generally of small patient numbers, diverse therapeutic strategies and diferent survival outcomes. Generally, patients with localized disease can have a 5-year survival of 50–60%, while relapsed and metastatic patients have a 5-year survival less than 20%.[14,15] The prognosis of PNETs depends on many factors, such as patient age, tumor site, tumor volume, metastatic disease, and treatment plans. The role of patient age in predicting disease outcome remains controversial. Substantial historical data from large randomized trials and large retrospective cohorts suggests that adults with Ewing family tumors do signifcantly worse than children, with 5-year OS rates ranging from 20 to 60% for localized disease[16-19]. However, many of these studies have focused on patients treated in the past century, before the advent of modern VDC/IE 5 drug regimen. In recent years, some centers reported a comparable outcome of their adult patients treated with modern multimodality therapy to outcome in children[20,21]. Difference in survival is caused by diference in treatment plans or intrinsic diference in tumor and/or host biology. Since past randomized clinical trials mainly focused on pediatric population, optimal therapeutic strategy for older adults diagnosed with Ewing family tumors remains to be defined.

In the literature, the role of extensive and complete or near complete surgical excision has been advocated as critical for local tumor control and prolonged survival.[22,23] Retrospective analysis of several large groups gives the impression of maximal local control when surgery is feasible[24]. Small round cell tumors such as Ewing's sarcoma family usually respond well to radiation[25]. Therefore, radiotherapy is frequently indicated for primary and adjuvant treatment of PNET. Radiotherapy as local treatment approach is used when complete local resection is not feasible with a functional organ, a difficult anatomic location, or with very large tumor volume not amenable to radical surgery even after neoadjuvant chemotherapy, and in case of a metastatic disease. Post-operative radiotherapy has been implied to decrease local recurrence and provide prolonged survival. The selection of local treatment modality is considerably biased by several factors, including tumor location, tumor volume, sensitivity to chemotherapy, patient general status, and institutional protocol. Some studies reported that radical radiotherapy as the only local treatment for Ewing's sarcoma predicted adverse survival or local control. However, in these studies, the choice of local treatment was influenced by multiple factors and thus non-randomized.

Thus it is difficult to establish clear guidelines for its management and treatment because of the minuscule number of reported cases. Its preoperative diagnosis is further complicated by the lack of specific imaging characteristics. Definitive diagnosis relies on postoperative pathology, immunohistochemistry, and genetic analysis. Early diagnosis and treatment of ES/PNET patients are thus highly challenging.

CONCLUSION

Extraosseous Ewing's sarcoma/primitive neuroectodermal tumors (ES/PNET) bladder primary tumor is a rare entity with a poor prognosis, hence an aggressive treatment combining surgery and chemotherapy must be considered from the beginning. Nevertheless, more cases must be published and analyzed for establishing diagnosis and protocolized guideline for the treatment of this disease.

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