Peripheral Primitive Neuroectodermal Tumor (PNET) of the Paravaginal Tissue

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Abstract- Peripheral primitive neuroectodermal tumor (PNET)is now considered an entity of Ewings sarcoma / primitive neuroectodermal tumor family .PNET of the female genital tract especially vaginal and paravaginal region is extremely rare.We present a case of a 29 year old lady with a paravaginal PNET diagnosed on histopathology and confirmed with the help of immunohistochemistry. Awareness of occurrence of PNET at unusual sites such as vagina is required to distinguish it from other tumors and for appropriate management.

Index Terms- PNET, Ewings sarcoma, Vagina

I. INTRODUCTION

Primitive neuro-ectodermal tumor (PNET) is a rare tumor comprising just about 1% of soft tissue sarcomas[1,2]. Primitive neuro-ectodermal tumors can be classified into central and peripheral according to the cell 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 tissues.[2,3] PNET is now 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 tumors that have a similar natural history, prognosis, immunohistochemical and cytogenetic profiles[3].

PNET of the female genital tract are extremely rare. The most common site of PNET in the female genital tract is the ovary followed by uterine corpus. Cervix, vulva and vagina being exceedingly rare.[2,8] . To the best of our knowledge only 8 cases of primary vaginal PNET has been reported in the English literature.[1,4,5]

We present a case of PNET of paravaginal tissue diagnosed by histopathology and confirmed with the aid of immunohistochemistry.

II. CASE REPORT

A 24 year old lady with an emergency Caesarian section done 6 months back presented with complaints of pain abdomen, nausea and fever since 30 days. Abdominal pain was initially confined to the right flank followed by generalized lower abdominal pain. Patient also gave a history of increased frequency of micturition and on and off white discharge per vagina. No history of weight loss or loss of appetite was present. . All investigations were within normal limits except for CA 125 and total LDH which were slightly raised. Per abdominal examination revealed a vague mass suprapubically with tenderness in the right iliac fossa. Vaginal examination showed mass in the right fornix, about 10x8cm, tensely cystic. Ultrasonography revealed a large lobulated mass lesion predominantly solid, with few cystic areas arising from cervix measuring 7.8x7.5cm, occupying the entire right vagina. Right ovary was not visualised.The tumor was biopsied and sent to pathology department as multiple grey brown to hemorrhagic tissue bits weighing 2gms.

Microscopic examination showed tumor composed of small cells with round to oval nuclei, fine chromatin, inconspicuous nucleoli, scant cytoplasm, abundant mitotic figures arranged in diffuse sheets with scant stroma showing dilated and congested blood vessels. PAS stain showed focal cytoplasmic positivity.

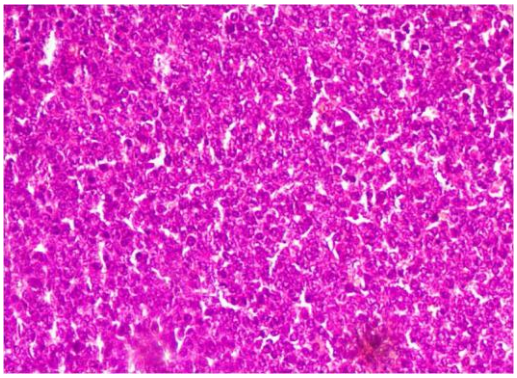

Fig 1.Diffuse sheets of small round cells H&E x 200

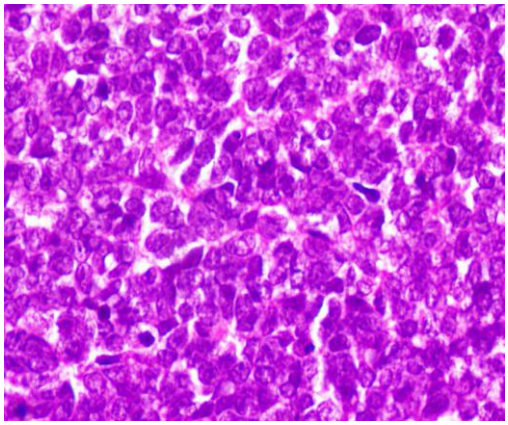

Fig 2 . Cells with fine chromatin, inconspicuous nucleoli, scant cytoplasm H&E x 400

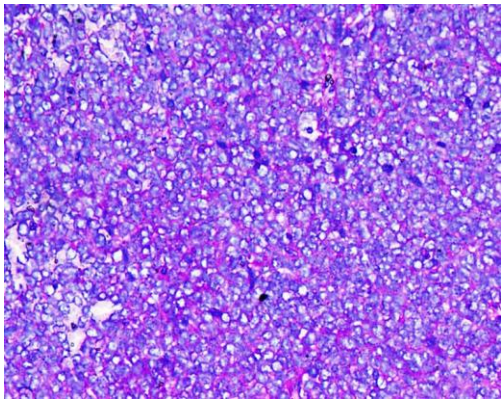

Fig 3 . Tumor cells show focal PAS positivity x 200

Immunohistochemistry showed tumor cells with strong membrane positivity for CD99, positivity for S100 (focal) and bcl2. Tumor cells were negative for Cytokeratin, Desmin, LCA, HMB45, Synaptophysin and Myogenin.

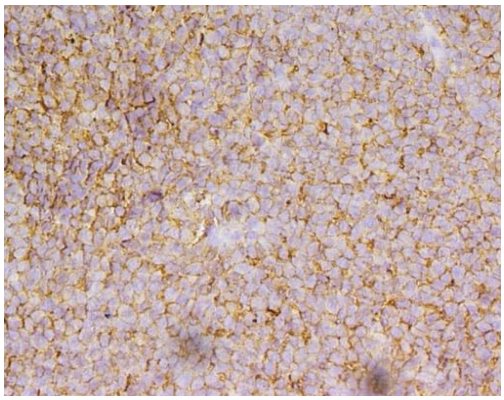

Fig 4 . Strong membrane positivity for CD 99 x 400

III. DISCUSSION

PNET was originally reported by Arthur Purdy Stout in 1918, on a tumor of the ulnar nerve with the gross features of a sarcoma but composed of small round cells focally arranged as rosettes and was initially termed neuroepithelioma[6].The term "primitive neuroectodermal tumor" (PNET) was first coined in 1973 by Hart and Earle. In the early 1970s the proposed criteria for the diagnosis of PNET included the clear association to a peripheral nerve and excluded disseminated neuroblastoma. The original description of PNET has evolved to include soft tissue masses even if grossly unassociated with peripheral nerves that meet a variety of proposed histologic, immunohistochemical, or ultrastructural criteria. Much controversy has surrounded this diagnosis primarily because of its similarity to other undifferentiated small round cell tumors.

Ewing sarcoma(ES) and PNET were regarded as distinct entities by themselves in the past. Recent developments point out that the small round-cell tumors seen in both tumor types share common phenotypic and molecular features, supporting the concept of a single tumor category [3], Ewing sarcoma/PNET family of tumors[4]. Ewing sarcoma/PNET, now defined as a group of small round-cell sarcomas that show variable degrees of neuroectodermal differentiation. Ewing sarcomas are tumors that lack evidence of neuroectodermal differentiation when assessed by light microscopy, immunohistochemistry, and electron microscopy in contrast to PNET that show neuroectodermal features when evaluated by one or more of the above modalities. Both, however, in 85% of reported cases are characterized by a t(11; 22) (q24; q12) chromosomal translocation leading to a chimeric transcript EWS-FLI1.[1,4,7,8] Peripheral PNETs show typical EWSR1 gene rearrangement, while central PNETs lack the EWSR1 rearrangement[1]. Its presence thus confirms a diagnosis of peripheral primary Ewing's sarcoma/ PNET, especially at unusual sites where the index of suspicion is low like the present case where it is rarely even considered as a differential.

PNET of the vagina presents usually as a rapidly growing painful deep mass. Symptoms of pain along with watery and foul smelling discharge per vagina and pressure symptoms such as tenesmus and difficulty in passing urine can be present. The age of previously reported cases of PNET of the vagina varied between 17 and 47 years old[2].Characteristic histological features including uniform small cells with round nuclei, fine chromatin, scanty clear or eosinophilic cytoplasm with glycogen content, and indistinct cytoplasmic membranes are common microscopic features . Although the presence of glycogen in a round-cell tumor was considered to be diagnostic, few cases may be glycogen-negative.

The usual differential diagnosis of paravaginal PNET includes poorly differentiated carcinomas, lymphomas, melanomas and sarcomas[5]. The absence of positivity for epithelial markers like cytokeratin helps in differentiating between carcinomas and to a lesser extent from small cell neuroendocrine carcinomas[5]. Lymphomas most closely resemble PNETs with sheets of malignant small cells without evidence of glandular or squamous differentiation.

Immunohistochemical markers currently used in the diagnosis of Ewing sarcoma/PNET family of tumors include MIC2 (also designated CD99), neurofilament proteins, neuron-specific enolase, vimentin, and HBA- 71. CD99 is expressed in the membranes of majority of Ewing sarcoma/PNET tumors. MIC2 expression has also been detected in lymphoblastic lymphoma and related leukemias, rhabdomyosarcoma, small cell carcinoma, Merkel cell carcinoma, mesenchymal chondrosarcoma and synovial sarcoma. However, MIC2 expression is a highly sensitive and reliable marker for the diagnosis of Ewing sarcoma/PNET when used as part of a panel of immunohistochemical stains, despite the lack of complete specificity[4]. The product of *MIC2* is a glycoprotein (also designated CD99 or p30/32MIC2) with a molecular mass of approximately 30,000 daltons located on the cell surface and believed to be involved in cell adhesion. Although immunohistochemical detection of membrane localized MIC2 expression is a sensitive diagnostic marker for the ES/PNET family of tumors, it lacks specificity in that many other tumors, and for that matter, many normal tissues, are also immunoreactive with anti-MIC2 antibodies. In addition, FLI-1 positivity is also helpful even though its expression is also noted in lymphomas, rhabdomyosarcomas and synovial sarcomas. Though more sensitive for synovial sarcomas, bcl-2 positivity

has also been documented in a subset of PNETs[1].MIC2 positivity is also identified in rhabdomyosarcomas and lymphomas. However, the lack of desmin, myogenin and MyoD-1 ruled out rhabdomyosarcoma in this case while LCA negativity ruled out a diagnosis of lymphoma.

The diagnosis of ES and PNET has been largely a process of exclusion. In recent years, detection and investigation of specific genetic alterations as has been discussed above have established exquisitely sensitive and specific markers for ES and PNET that have rapidly become the standard for confirming the diagnosis.

IV. CONCLUSION

Our case being one of the very rare locations of the PNET reinforces the value of histopathological examination and IHC in the objective identification of this sarcoma at unusual sites like the vagina. However, preoperative diagnosis is often very difficult to establish. The importance of correct diagnosis and identification of the tumor helps in early institution of appropriate management [1]. Multimodality therapy is used in most, including radical surgical resection and irradiation being the current treatment of choice[9].The treatment outcome for patients with primary vaginal Ewing's sarcoma/PNET has been favorable in so far as documented cases are concerned with a 5 year survival rate of 24-80% in small resectable cases and showing better prognosis than the PNETs in the other parts of the female genital tract[1,5].

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