PRIMITIVE NEUROECTODERMAL TUMORS AT UNCOMMON SITES- A REVIEW OF 6 INTERESTING CASES IN VARIED LOCATIONS

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Sir,

Primitive neuro ectodermal tumors (PNET) and Ewing's sarcoma are aggressive malignant tumors affecting children, adolescents and young adults. Tumor cells in these lesions are classically described as small round blue cell tumours (SRBCT) on histology. We report a series of small round cell tumor diagnosed to be PNETs on histopathology (Figure 1) in six different sites - lung, maxilla, spine, rib, finger and kidney.

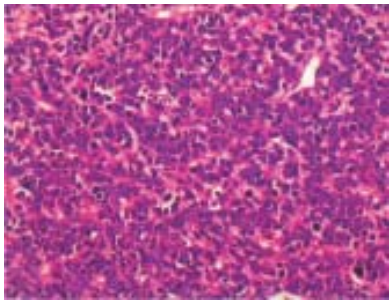

Figure 1: Tumor composed of small round blue cells arranged in sheets (Haematoxylin and eosin stain x 200)

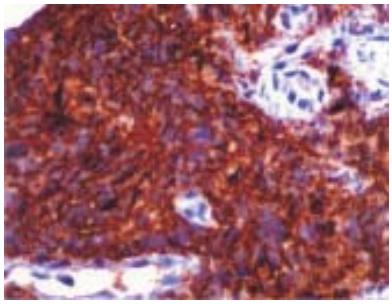

Figure 2: Cytoplasmic membrane staining in tumour cells (Immunostain CD99 X 200)

The clinical presentation of each of these cases is summarised in table 1. Immunomarker CD 99 played a vital role in providing a conclusive diagnosis (Figure 2) in these cases.

There is a considerable clinical and histologic overlap between PNET and Ewing's sarcoma and hence they are grouped together. Generally, Ewing's sarcomas arise within the bone, while PNET occurs within soft tissues. However, diagnostic difficulty arise when Ewing's sarcoma occurs within soft tissue (Extraosseous Ewing's Sarcoma) and vice versa. Tumor cells of both lesions share a considerable homology though only PNET exhibits neuroendocrine features. Ewing's Sarcoma is considered to be a more undifferentiated tumor than PNET.

The Ewing's Sarcoma/PNET group of tumors are characterized by non- random chromosomal translocations involving the EWS gene and one of the transcription factors. The translocation t(11;22)(q24;q12) is the most common

Table I: Summary of clinical presentation and histopathological findings

S.No.	Age/sex	Location	Clinical presentation	HPE diagnosis	IHC markers	Final diagnosis
1	42/Male	Anterior chest wall	Swelling 1year duration	SRBCT- Rib	CD 99: + ve S 100 ;EMA ;CK: -ve	PNET
2	3/Female	Cheek	Left cheek swelling	SRBCT- Maxilla	CD 99: + ve CD 45 ; CD 3;CD 20;CK; Desmin: -ve	PNET
3	17/Female	Thoracic spine	Paresthasia, both lower limbs – 10 days	SRBCT- Thoracic spine	CD 99 : + ve CD 45: -ve	PNET
4	43/Female	Lung	Fever, chest pain and cough – 1week	SRBCT- Lung	CD 99: + ve CD45;CD20;CK;Chromogranin; Synaptophysin :-ve	PNET
5	19/Male	Little finger	Pain & swelling over the right metacarpal joint	SRBCT- Little finger	CD 99 : + ve CD 45; CD117;SMA :-ve	PNET
6	25/Male	Kidney mass	Loin pain	SRBCT- Kidney	CD 99 : + ve CK; CD 45; Chromagranin: -ve	PNET

+ ve: Positive ; -ve: Negative
SRBCT: small round blue cell tumours

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one and leads to the formation of the EWS- FLI 1 fusion protein, which contributes to the pathogenesis of Ewing's Sarcoma/PNET modulation and expression of the target genes. [1] Real time polymerase chain reaction (RT-PCR) and Fluorescence in situ hybridization (FISH) are molecular diagnostic tests commonly used to detect the presence of this specific translocation. On light microscopy, PNET shows sheets and large nests of uniform, small, round to polygonal cells with scant cytoplasm and indistinct cell borders. Nuclei features dispersed chromatin with hyperchromasia and variable mitotic figures. Rosettes may be present in 10% of the cases. These cells are positive for PAS (Periodic acid Schiff) stain due to the presence of glycogen in the cytoplasm. Areas of haemorrhage and vascular lakes or sinuses may also be present with areas of geographic necrosis.

Ewing's sarcoma/PNET are also shown to frequently express cytokeratin suggesting partial epithelial differentiation. Schuetz et al examined the immunostaining for claudin 1, occludin, zonula occludens-1, desmoglein, desmoplakin and E Cadherin in cases of PNET.[2] CD99 (MIC 2) is an important immunomarker for identification of this tumor with membrane staining in tumour cells. This is a useful tumour marker when used as a part of panel of immunostains that are negative in PNET (CD20, CD45, CD3, Desmin). Focal positivity is seen for synaptophysin while keratin, chromogranin, desmin and neurofilament protein are negative. Ultrastructurally the tumour cells reveal neurosecretory granules and cytoplasmic processes.

The differential diagnosis for small round blue cell tumors include PNET and other small blue cell tumors: mesenchymal chondrosarcoma, non Hodgkin's lymphoma, neuroblastoma and small cell osteosarcoma.[3] To rule out these possibilities, immunomarkers play a pivotal role. Positivity for S100 protein suggests mesenchymal chondrosarcoma, while immunopositivity for CD 45 and monoclonality for T or B cell marker confirms a non Hodgkin's Lymphoma. Neuroblastoma shows immunopositivity for synaptophysin and chromogranin. CD 99 by itself is non specific and hence neural markers like neuron specific enolase (NSE), electron microscopy and image cytometry should also be utilised to conclude the diagnosis of PNET.[4] Demonstration of the reciprocal translocation of the chromosomal 11 and 22 confirms the diagnosis. Mhawech et al have suggested a combination of CD 99 immunostain and FLI 1p for a precise diagnosis of EWS/PNET. [5]

The prognosis of ES/PNET is determined by the outcome of the metastatic disease rather than local control of tumour. Favourable prognostic factors are age less than 10 years, distal extremity, volume of tumor less than 100ml and chemotherapy response prior to resection. The unfavourable factors are tumour in the pelvis, tumor size more than 8cm, elevated WBC count and ESR. Over-expression of tumour suppressor gene p53, cell proliferation nuclear antigen, Ki67 and Her 2neu are associated with poor prognosis. Chemotherapy with ifosfamide, etoposide, vincristine, doxorubicin, cyclophosphamide, dactinomycin in various combinations are used for therapy in these cases.

To conclude, in centres unequipped with molecular detection methods, histopathology and immuno-histochemistry play an important role in the diagnosis of this aggressive neoplasm.

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