A case series of Extraosseous Ewing's Sarcoma

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Extra-osseous Ewing's sarcoma (EES) represents about 5% of the Ewing family of tumors. EES is a rare entity occurring predominantly in adolescents and young adults, usually arising from the soft tissues of the trunk or the extremities, with no evidence of malignancy on skeletal scintiscan or bone marrow aspirate. We report 4 unique cases of EES, their rare presentation, diagnostic dilemma and their treatment options.

CASE REPORTS:

CASE 1:

A 16-year-old male was evaluated for the complaints of blood in urine and a vague abdominal pain of 1-month duration. CT Abdomen showed a mass arising from the right kidney encasing the right renal vessels and infiltrating the right lobe of liver. There were multiple skeletal metastases, paravertebral and pre-vertebral soft tissue mass and multiple sub pleural nodules.MRI (Magnetic Resonance Imaging) Thorax and Abdomen confirmed the infiltrative right renal mass with multiple cystic lesions. The tumor mass was seen infiltrating right renal vessels and right lobe of liver with retroperitoneal nodes and pulmonary metastases.

Biopsy from the mass in the right adrenal/kidney upper pole showed linear cores of malignant neoplasm with areas of necrosis and nests of hyperchromatic small cells with high nuclear cytoplasmic ratio against a desmoplastic stroma with focal rosette like structures suggestive of malignant small round cell tumor. Immunohistochemistry was positive for cytokeratin, chromogranin and FLI 1 (Friend leukemia integration 1) suggestive of Ewing's Sarcoma.

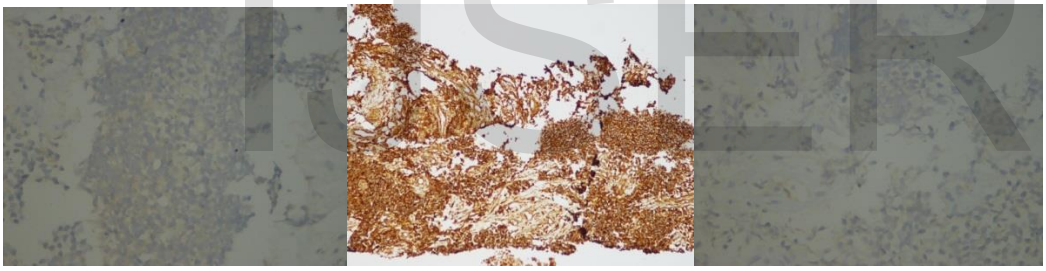

Fig. 1 100x magnification *a)* CD56 negative tumor cells *b)* showing tumor cells with diffuse membranous and cytoplasmic positivity for CD99 *c)* chromogranin negativity

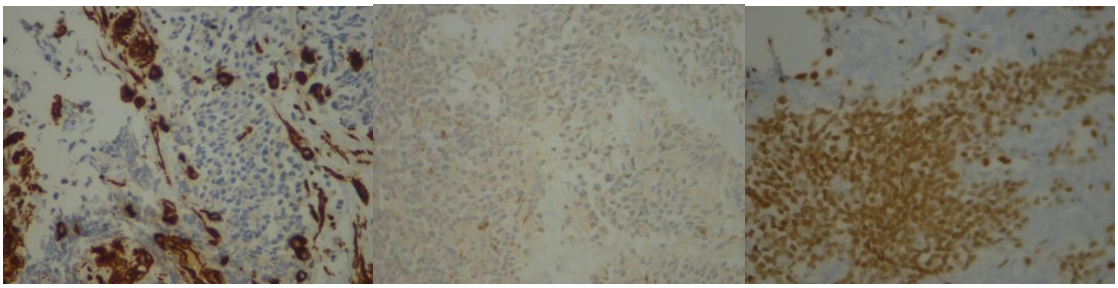

Fig. 2 400x magnification *d)* focal cytoplasmic positivity of vimentin *e)* focal cytoplasmic positivity of cytokeratin f) strong nuclear positivity of FLI-1

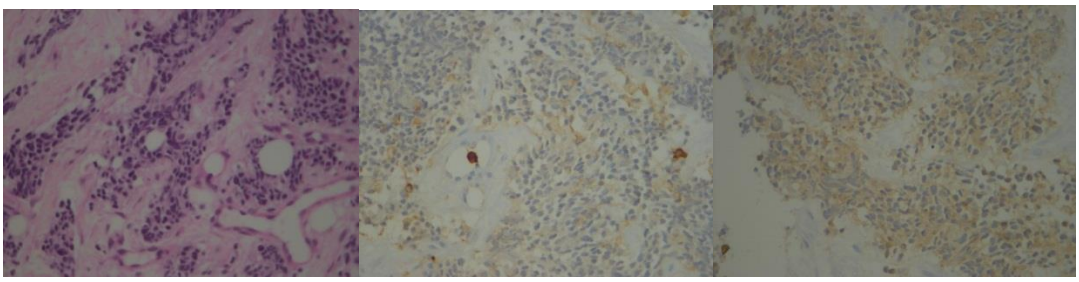

Fig. 3 100x magnification *g)* Tumor cells arranged in sheets, nests and vague rosettes having scant eosinophilic cytoplasm and round hyperchromatic nucleus *h)* LCA negativity *i)* Weak and focal positivity of synaptophysin

He was treated with 6 cycles of VIDE regimen chemotherapy (*Vincristine 1.5 mg/m2 D1; Ifosfamide 3 g/m2 D1-D3; Doxorubicin 20 mg/m2 D1-D3; Etoposide 150 mg/m2 D1-D3).*

Post-chemotherapy PET-CT (Positron Emission Tomography-Computed Tomography fusion) showed a non FDG avid, residual, well defined heterogeneously enhancing soft tissue mass with amorphous calcification arising from the upper and interpolar region of the right kidney with residual enhancing renal tissue in the lower pole measuring 6.3 x 6.4 x 4.5 cm compared to the pre-chemotherapy size of 17 x 12x 11.3 cm. The mass was abutting the right renal vessels and infiltrating the right adrenal gland without crossing the midline. The extension to right lobe of liver, crus of right diaphragm and the right psoas muscle had resolved. The collapsed D3 and L5 vertebral body with sclerosis, the lytic lesions in multiple cervical, dorsal, lumbar and sacral vertebrae, bilateral iliac bones and sclerosis of left inferior pubic ramus with adjoining periosteal reaction also were not FDG avid.

MRI Abdomen obtained a month later showed well defined heterogeneously enhancing soft tissue mass arising from upper pole of right kidney having regressed marginally, measuring 3.5 (AP)x 6.0 (T)x 6.2 cm (CC) with infiltration of adrenal gland, abutting the origin of psoas muscle posteriorly and no extension into renal vein or pelvi-calyceal system.MRI spine showed stable vertebral metastases.

He underwent Radical Nephrectomy. Post-operative histopathology showed residual foci of poorly differentiated malignant tumor. The surgical bed was irradiated with 50.4 Gy in 28 fractions over 4 weeks using 6 MV photons by Image Guided Radiation Therapy. Post-operative computed tomographic (CT) images can be seen in Fig. 1, Fig. 2; External Beam Radiotherapy Treatment planning can be seen in Fig. 3

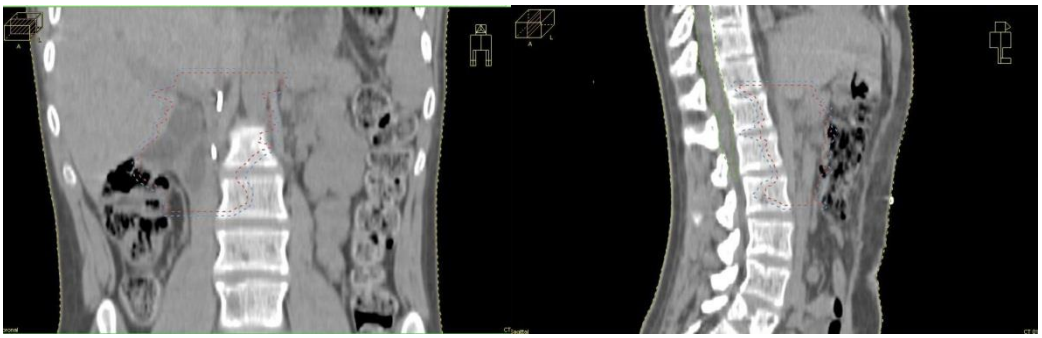

Fig. 4 Post-surgery CT Abdomen Sagittal and Coronal views

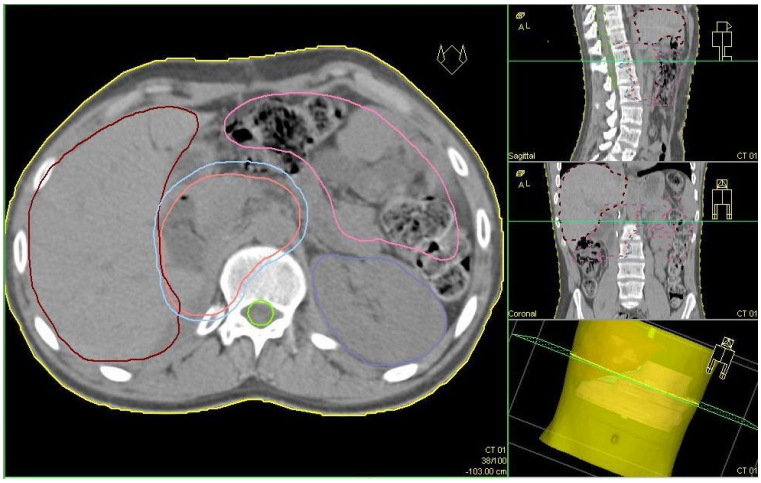

Fig. 5 External Beam Radiation Planning for Renal Bed post-surgery

He was on regular follow-up. 8 months post-radiation, he presented with left iliac bone pain. PET-CT revealed an increased FDG uptake in the left ilium with no metabolically active disease elsewhere. Left ilium bone marrow aspiration and biopsy revealed complete infiltration with small round blue cells suggestive of disease recurrence. Due to the recurrence of disease, poor prognosis and chances of survival, he was treated with metronomic chemotherapy and palliative care.

This is a rare case of EES arising from the renal parenchyma in a young male presenting with extensive metastases with a progression free survival of more than 10 months following aggressive multimodal management and prolonged survival. He is still on follow-up 20 months after diagnosis

CASE 2:

A 45-year-old male was evaluated for abdominal pain, with a few episodes of vomiting for 6 months with no other significant symptoms by September 2018.

He initially underwent an UGI (upper gastro intestinal) scopy and was found to have a smooth bulge in the body of the stomach. CT abdomen revealed a non-calcifiedheterogeneous irregular mixed solid cystic mass of size 7.6 x7.4 cm in the body and tail of pancreas. The fat plane between the greater curvature of body of stomach and the mass was lost, with infiltration into the outer layers of the stomach. There was direct infiltration into the distal splenic vein in the pancreatic bed with a non-occlusive thrombus in the distal splenic and proximal main portal vein for a length of 4 cm. Three heterogeneously enhancing irregular nodules of 1-3 cmwere seen in both lobes of liver. Imaging were suggestive of malignant neuroendocrine tumor.

Core needle biopsy of segment V of the liver lesion showed small round cell pattern with nuclear to cytoplasmic ratio with vesicular nuclei and few cells also showing prominent nucleoli. Mitoses is of 7/10 HPF (high power field).

The differentials including a neuroendocrine tumor and thelocation, prompted a Gallium 68- DOTANOC scan. It revealed a non-avid pancreatic lesion with retroperitoneal nodes and non-avid lesions in the both lobes of the liver with largest lesion of size 5.3 x 4.1 cm in the segment VI of liver.

It was discussed in the tumor board and in view of high Ki67 and clinical and radiological picture suggestive of Pancreatic Neuroendocrine tumor patient was initially started on VP16/CDDP chemotherapy with palliative intent.

Further analysis of the specimen (Immunohistochemistry) revealed CK positivity with FL1 diffuse nuclear positivity with CD99 diffuse strong membranous positivity, vimentin focal positivity and ki67 45-50, consistent with Ewing's sarcoma/primitive Neuroectodermal tumor(PNET).EWSR1 (22q12) gene rearrangement by FISH was positive confirming the diagnosis of Ewing's sarcoma/PNET.

After confirmation with molecular cytogenetics, the patient was recounselled regarding the diagnosis of Ewing's sarcoma/PNET and was started on alternating cycles of VAC/IE regimen.

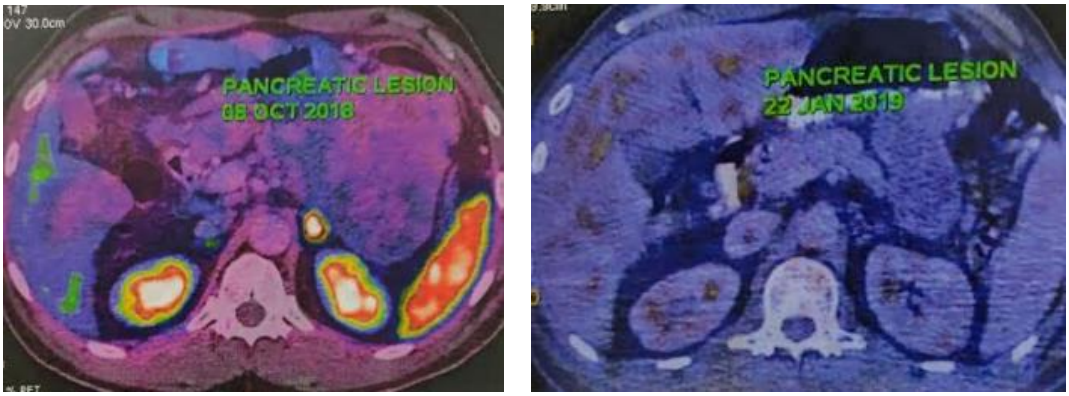

Fig. 6: showing pancreatic body and tail lesion by october 2018 and after 4 cycles of alternating VAC/IE chemotherapy showing reasonable good response by janurary 2019.

He is tolerating the treatment well and hada documented response to the same for almost 10 months and he was lost for follow up

This case highlights the dilemma in diagnosis and hence the delay in the definitive treatmemt. A high level of suspicion is necessary for any soft tissue lesion with small round cell features.

CASE 3:

A 40 year old lady was evaluated for vague abdominal pain on the left side for 6 months. PET CT scan showed a metabolically active lobulated heterogeneously enhancing retroperitoneal soft tissue attenuation mass lesion in left paraaortic region with infiltration of left ureter and surrounding mild fat stranding. There was moderate proximal hydroureteronephrosis with diffuse thinning of left renal cortex. The lesion was abutting the left psoas muscle with suspicious infiltration. It was found to partially encase the distal abdominal aorta and proximal left common iliac artery. There was a metabolically active peritoneal nodule in right paracolic gutter.

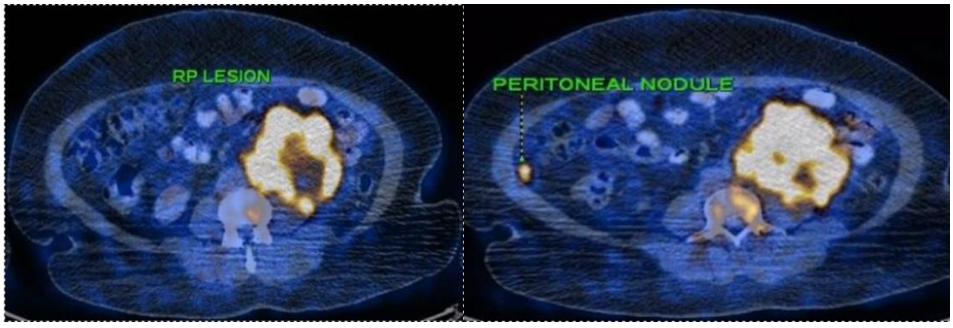

Fig 7: PET CT showing the left para vertebral mass and the peritoneal nodule

A core needle biopsy done elsewhere was suggestive of a small round cell tumor. DTPA scan showed nonfunctioning left kidney. The biospy specimen was inadequte for futher IHC and molecular studies. A repeat core biopsy was done and the IHC was suggestive of Ewings tumor/Primitive Neuroectodermal Tumor.

She received 6 cycles of alternating VAC and IE chemotherapy. PET CT scan showed a complete resolution of metabolic activity. She underwent surgery for the residual lesion. HPE of the residue showed fibrosis with no active disease. She completed her adjuvant VAC/IE chemotherapy and he is on follow up 18 months post diagnosis.

This case highlights the need for a high level of suspicion in a soft tissue lesion and adequacy of tissue sampling. It is a representation of a good response following defintive treatment.

CASE 4:

A 26 year old lady presented with a right thigh swelling of 2 ½ month duration by october 2018. MRI of the Rightthigh showed a Large heterogeneous ovoid lesion with ill -defined margins in the Right inner thigh; located in the subcutaneous plane, indenting the underlying muscle. There was heterogeneous appearance noted with small areas of necrosis / liquefaction within the mass with marked internal vascularity noted with the vessels showing a distorted appearance. It was suspicious of a Sarcoma.

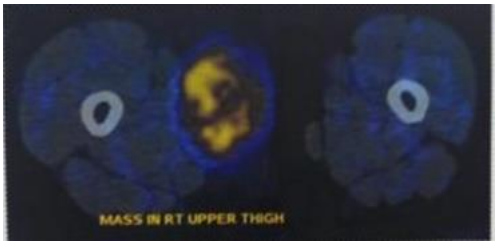

fig.8: showing a right thigh mass in the soft tissue without any bone involvement

FNAC was suggestive of a probable Malignant PNET / Extra skeletal Ewing's / Alveolar soft part sarcoma. Trucut biopsy from the Right thigh swelling was suggestive of a Malignant small round cell tumor. IHC showed Cytokeratin Negative, Vimentin Positive, Synaptophysin Positive in few cells, DesminNegative,CD99: Positive (Diffuse Membranous), FLI-1 Positive (Diffuse), LCA Positive in background Lymphocytes and TDT Negative, which were consistent with Ewing's sarcoma/ Primitive neuroectodermal tumour. She received 4 cycles of neoadjuvant chemotherapy with alternating VAC/IE chemotherapy. She tolerated the chemotherapy well and physically the mass grossly reduced and became impalpable. She then underwent a wide local excision, HPE showed minimal microscopic residual disease. She continued her adjuvant chemotherapy and completed 14 cycles of VAC/IE chemotherapy and is disease free and on follow up till now for 2 years.

DISCUSSION:

Ewing's Sarcoma is the seond most common bone tumor in children. It was first described by Ewing in 1921.(1) Extra skeletal Ewing's sarcoma are soft tissue neoplasms, similar to their skeletal counterparts morphologically. They were first described by Angervall and Enzinger in 1975. (2)

They are characterized by their rarity. The common sites of occurrence were found to be the chest wall, paravertebral region, retroperitoneal space, lower extremities, and gluteal region. The kidney, breast, gastrointestinal tract, prostate, endometrium, the adrenal glands, brain, and lungs are the other rarer sites that have been reported.(3)

They seem to have an later and bimodal presentation with male preponderance. They have been more commonly diagnosed as a PNET rather than an Ewings'sarcoma.(4) EES by itself seems to be a poor prognostic feature, manifesting with inferior survival rates. (5) However, for localised disease, this seems to be the same as that of their skeletal counterparts. This can be explained by advanced stage of presentation of the EES and the delay in diagnosis.

Radiologically they are found to heterogenously enhancing on CT scan with occasional hypodense necrotic areas. In an MRI, they are hypo to iso intensein a T1 weighted image, hyper intense on a T2 weighted image and heterogenous enhancement with contrast. PET CT scan has not been found to be of much use.(6)

Histopathologically, they are found to have poorly differentiated small round cells. They need to be differentiated from metastatic neuroblastoma, alveolar rhabdomyosarcoma, metastatic small cell carcinoma, PNET and malignant lymphoma. Ewing's sarcoma and PNET have similar characteristics and are difficult to be differentiated by light microscopy. (7)They stain positive for CD 99, FLI1, Vimentin and Cytokeratin. Although both ESS and PNET show expression of HBA-7 and the t(11:22) translocation, only ESS contains PAS-stained glycogen in the cytoplasm. The cytogenetics show translocations involving the EWSR1 gene at 22q12 and either the FLI1 gene at 11q24 or the ERG gene at 21q22 (8) The most common gene fusion being the EWSR1-FLI1 (90% to 95% of patients). This seems to be diagnostic of Ewing's sarcoma.

In our cases, renal and Pancreatic locations made the diagnosis difficult. There are a few cases reported in the literature.(9) There are only about 24 cases of pancreatic Ewing's sarcoma that have been reported. (10)

The diagnosis of an EES is by a high degree of suspicion coupled with the necessary radiology and pathology investigation. Delay in arriving at the correct diagnosis have always delayed the appropriate treatment for patients, as was the case in our patients also. The fact that localized diseases do equally well as the skeletal Ewing's sarcoma, warrants an aggressive multimodality management involving Surgery, chemotherapy and radiotherapy as and when required.(11)

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