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Diffuse S-100 Positive Skeletal Ewing Sarcoma: A Rare Diagnostic Enigma

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Abstract

Ewing Sarcoma is a malignancy which presents usually in the 2nd or 3rd decade of life in the axial skeleton. Immunohistochemistry is used to differentiate this diagnosis from other round blue cell tumours such as neuroblastoma, medulloblastoma etc., which show similar morphology on light microscopy. Diffuse S100 staining is not considered to be positive in this malignancy and such an occurrence mandates diagnostic confirmation by genetic tests such as Fluorescent in situ hybridization. Here we present a case of a EWSR1 gene rearrangement proven case of skeletal Ewing Sarcoma with diffuse S100 positivity in a middle-aged female hailing from Northern Pakistan.

Background

Sarcomas form a comparatively rarer group of malignancies with bone origin sarcomas having an even rarer incidence [1]. The incidence of skeletal Ewing Sarcoma has been recorded to be about 2.6 per million in the peak incidence age group of 15-29 years [1]. EWSR1 gene rearrangement has been commonly found in these patients with the commonest rearrangement as EWSR1:FLI1 in 85% of cases [1]. Ewing sarcoma has been diagnosed most commonly in the axial skeleton with the pelvic girdle (22%) having the highest proportion [1].

Histopathologically Ewing Sarcoma specimens show small round blue cell morphology and further immunohistochemistry is carried out with CD99 showing strong membranous positivity [1]. Commonly, S100 shows no staining and even if it does, only weakly [2].

Here we present a case of a skeletal Ewing sarcoma which was diffuse S100 positive with confirmed diagnosis after detecting gene rearrangement of EWSR1.

Case Summary

Patient is a 40 year old female, Para 9+0, with no known comorbids or addiction history and no significant family history for any malignancy who had presented at the hospital with swelling at the base of the right thumb. She was in her usual state of health until 4 months back when she noticed that her right thumb was dislocated, however it remained uninvestigated at that time. Two months back she developed a painful swelling at the base of the right thumb which was increasing in size but had no associated discharge.

On examination, there was a middle-aged female with healthy build. There was a 6 × 6 cm firm swelling at the base of the right thumb which was extending into the thenar eminence (Figure 1a, b, c). The overlying skin was comparable to the rest of the body. No motor activity was seen in the thumb with absent sensitivity to touch. However, there was adequate capillary refill indicating intact blood supply. There was normal bilateral vesicular breathing and rest of the systemic examination was unremarkable. MRI with contrast showed a 4×4.3×3.9 cm mass centered at the 1st metacarpal causing destruction of the bone with soft tissue component. No lymphadenopathy or direct involvement of the neurovascular bundle was seen; however the lesion was closely abutting it (Figure 2a, b, c).

USG guided trucut biopsy of the lesion showed a malignant neoplasm composed of sheets and nests of hyperchromatic cells with brisk mitotic activity and necrosis (Figures 3, 4 and 5).

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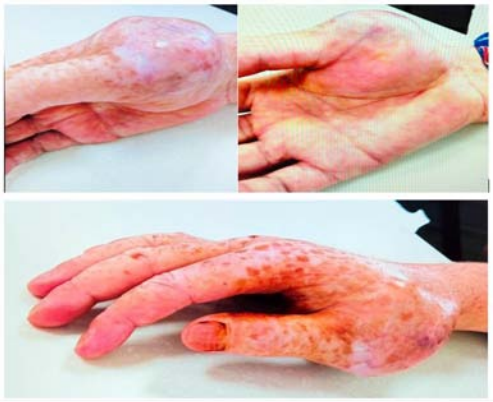

Figure 1a-c: Pre-treatment images of the lesion on examination.

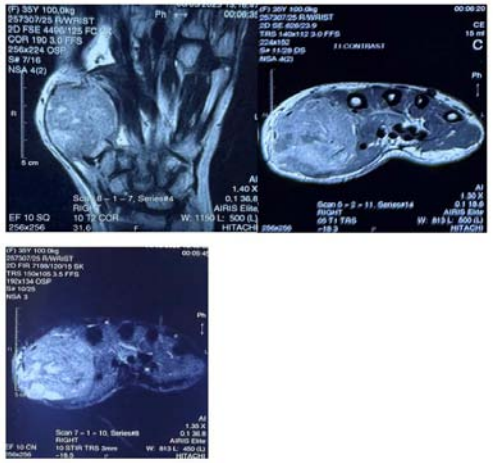

Figure 2: Pre-treatment MRI in T2 coronal (a), T1 (b) and STIR (c) sequences.

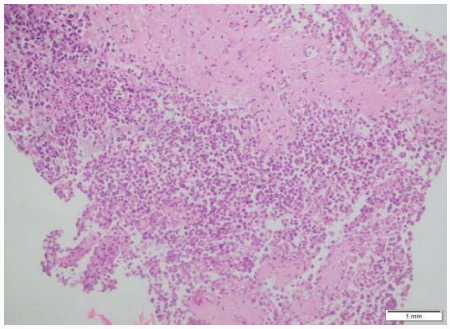

Figure 3: Photomicrograph showing H&E stain x40.

Immunohistochemistry showed S100 diffuse nuclear and cytoplasmic staining (Figure 6), CD99 showed diffuse membranous staining (Figure 7), NKX2.2 showed diffuse nuclear staining (Figure 8), EMA was weak patchy positive, there was retained expression of INT1 and was negative for LCA, CK, CD138, TFE3, HMB45 and Desmin. This was diagnosed as a case of Ewing sarcoma. Diffuse S100 positivity is an unusual finding in Ewing Sarcoma hence a further FISH test (Fluorescent in situ hybridization) for EWSR1 break-apart was conducted which detected the presence of EWSR1 gene rearrangement on paraffin embedded formalin fixed tissue (Figure 9). This confirmed the diagnosis of Ewing Sarcoma.

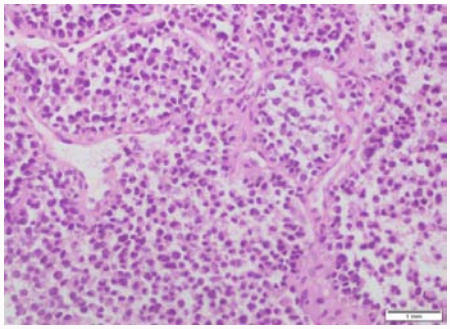

Figure 4: Photomicrograph showing H&E stain x100.

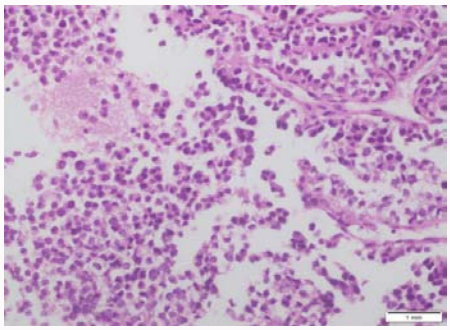

Figure 5: Photomicrograph showing H&E stain x400.

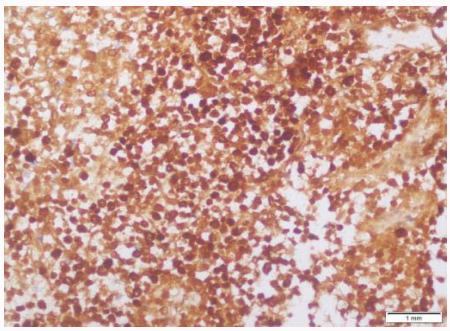

Figure 6: Photomicrograph showing Diffuse S100 nuclear and cytoplasmic staining.

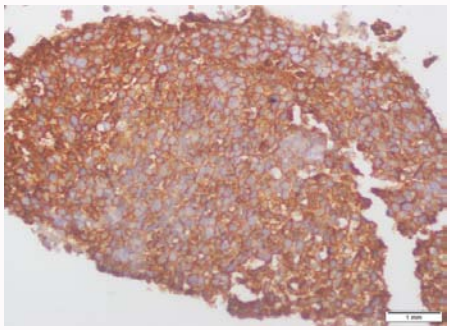

Figure 7: Photomicrograph showing Diffuse CD99 membranous staining.

CT scan chest showed a small tiny suspicious nodule at lateral segment of right middle lobe measuring 2.6 mm which after review with a certified radiologist was said to be kept on follow up and not currently declared as metastatic.

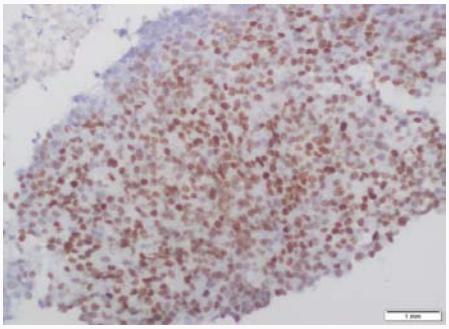

Figure 8: Photomicrograph showing Diffuse NKX2.2 nuclear staining.

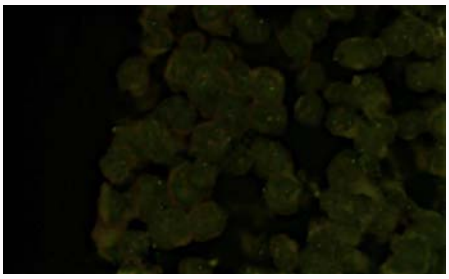

Figure 9: FISH test showing EWSR1 gene rearrangement.

According to the AJCC 9th edition TNM staging system, she was staged as cT1 (Tumour size 8cm or less in greatest dimension), cN0 and cM0 with no histopathological grading (GX) and hence grouped as stage IA.

She was planned for systemic chemotherapy consisting of 3 cycles of VAC (Vincristine, Doxorubicin and Cyclophosphamide) alternating with IE (Ifosfamide and Etoposide), followed by restaging and plan for surgery or radiation therapy. She has received 1 complete cycle of VAC/IE at the time of this publication with good clinical response seen with evident regression in the size of the lesion.

Discussion and Conclusion

Ewing sarcomas arise from a family of small round blue cell tumours which share general similar morphological features under the light microscope of small round cells with scanty cytoplasm and stain blue/purple when the Heamatoxylin and Eosin stains are used [3]. This family of tumours comprises of but not limited to Ewing sarcoma, Neuroblastoma, Medulloblastoma, Small cell lung cancer, Merkel cell carcinoma, small-cell lymphoma, mesothelioma, synovial sarcomas etc [4]. This wide variety of morphologically similar but behaviorally variable tumours makes it vital to have an accurate diagnosis as this has an important implication in the management and prognosis of patients.

Immunohistochemistry (IHC) is being used by pathologists globally to tackle this challenge and over the decades, general agreement on the IHC patterns of various tumours have been discovered and established. However, exceptions and rare occurrences can be seen and they can pose a challenge to pathologists and the treating physicians.

Ewing Sarcoma has been generally described as showing the following IHC patterns:

1. Diffuse membranous expression of CD99 in 90-95% of cases
2. NKX2.2 (high specificity)
3. Vimentin in 80-90% of cases

These positive staining results are complemented with negative staining patterns of LCA/CD45, Desmin, Myogenin, WT1, S100, Syntaptophysin, Cytokeratin, CD56 etc. in the majority of cases [2].

S100 is an IHC marker which is found mainly in tumour cells of neural crest origin such as melanoma, nerve sheath tumours, clear cell tumours of soft tissue, glial tumours etc [5]. Ewing sarcoma tumour cells generally do not show any positivity for S100 as mentioned above, however if it does show positivity, it is weak and focal.

There are however very few cases reported in the literature which described diffuse and strong staining of S100 in these tumours [6,7]. This makes it imperative to confirm the diagnosis of Ewing sarcoma with genetic investigations such as the FISH test for EWSR1 gene rearrangement.

With the aid of targeted literature search in PubMed using the terms of "diffuse S100 positivity" and "Ewing Sarcoma", we discovered published reports on cutaneous and other extra-skeletal molecularly confirmed cases of Diffuse S100 positive Ewing sarcomas and no such case of skeletal origin has been found. Our case described here is to our knowledge the first case of confirmed EWSR1 gene rearrangement skeletal Ewing Sarcoma with diffuse S100 positivity.

To further add rarity to our case is the fact that it has presented at an unusual age (40 years) and at an unusual location (1st metacarpal) as skeletal Ewing sarcomas usually present in the 2nd to 3rd decade of life in the axial skeleton.

In conclusion, we would like to emphasize that even though malignancies such as Ewing Sarcoma are a less likely diagnosis in diffuse S100 positive round blue cell tumours, genetic testing should become a part of the complete diagnostic workup to avoid a misdiagnosis and wrong treatment.

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