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CASE REPORT

Post-Chemotherapy Neuroblastoma-like Differentiation in Ewing Sarcoma of Humerus: Report of a Rare Case with Review of Literature

Nasir Ud Din[1], Amna Qasim[2], Zubair Ahmad[1] and Sheema Hasan[1]

ABSTRACT

A 21-year patient initially presented with a fracture of the humerus following minor trauma. A bone scan and biopsy were done due to the suspicion of pathological fracture and the biopsy confirmed the diagnosis of Ewing Sarcoma (EWS). Two months after initial presentation, chemotherapy was started and 5 cycles were given over a span of 6 months. Surgical resection of the tumor was then performed. The post-chemotherapy resection specimen, on histological examination, showed the presence of areas of neuroblastoma-like differentiation in otherwise morphologically classic EWS. Cytogenetic analysis by FISH revealed EWSR1 gene rearrangement. Four similar cases have been reported earlier in literature, all in females below 20 years of age. Our case is unique as it is the first case of post-chemotherapy neuroblastoma-like differentiation of EWS in a 21-year male.

Key Words: *Ewing sarcoma. Neuroblastoma. Neural differentiation. EWSR1. CD99.*

INTRODUCTION

Ewing sarcoma (EWS) is the second most common primary malignant bone tumor.[1] It is characterized by small round cells with basophilic nuclei, scanty cytoplasm, and brisk mitotic activity. Rearrangements of the EWSR1 (Ewing sarcoma breakpoint region 1) gene on the 22q12 and related oncogenes, most commonly FLI1 on 11q24, are detected in about 90 to 95% of these tumors.[2]

Neural/neuroectodermal differentiation may be seen in EWS/PNET which is histologically evident as rosette-like structures, and/or ganglionic differentiation. These structures demonstrate variable immunoreactivity for neural markers, such as neuron specific enolose (NSE), CD57, S100 protein, synaptophysin, and PGP9.5.[3] This suggests a link between EWS/PNETs and neuroblastomas (NB). Cytogenetically, neuroblastomas do not show (11;22) translocation or its variants. They are rather, characterized at a cytogenetic-molecular level by deletion or rearrangement of the short arm of chromosome 1, amplification of N-MYC (neuroblastoma-derived myelocytomatosis oncogene), and gain of chromosome 17q1p.[4] Histologically, NBs show a broad spectrum of differentiation, ranging from undifferentiated tumors composed only of small round cells without neuroblasts or neuropil formation, to the most differentiated tumors showing partial or complete ganglionic differentiation. Unlike EWS/PNET, NBS do not express CD99.[4]

Post-therapy neural differentiation of the EWS/PNET is a very rare event and to the best of our knowledge, only 4 cases have been reported in literature, all in females below 20 years of age.[2,5-7] Here, we present to our best of knowledge, the first case of post-therapy NB-like differentiation in a male patient of 21-years.

CASE REPORT

A 21-year male presented with a history of fracture of the right humerus following minor trauma during a sports activity. A bone scan was performed two months after the initial presentation and it demonstrated increased uptake at the right shoulder joint, distal two-thirds of the shaft of right humerus and adjacent proximal end of right radius. There was no evidence of distant skeletal metastases. MRI showed an abnormal heterogenous mixed signal destructive lesion measuring 15x6.1x5cm with a soft tissue component and surrounding bone edema at humeral diaphysis extending down to the metaphysis with sparing of epiphysis. A biopsy of the bone was taken at the same time which showed a small round blue cell tumor (Figure 1A) exhibiting cytoplasmic glycogen on PAS stain and strong membranous staining for immunohistochemical stain CD99. Leucocyte common antigen (LCA), TdT, desmin, and synaptophysin were negative. It was reported as EWS, based on morphological and immunohistochemical features.

CT scan of the abdomen/pelvis was normal. However, CT scan of the lungs revealed a small nodule in the

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posterior basal segment of the lower lobe of the left lung, raising suspicion of possible metastases.

Chemotherapy was started and 5 cycles of VAC/IE (Vincristine, Actinomycin D, Cyclophosphamide/ Ifosfamide, Etoposide) were given over a period of 6 months. MRI of the right arm, performed after 4 cycles of chemotherapy, showed a slight reduction of tumor size which now measured 13x6.1x5cm. There was a significant reduction in the swelling, but the hard component remained the same. The patient was admitted for an elective right humerus wide margin resection plus a vascularized fibular graft and flap surgery.

The excised specimen comprised of a segment of humerus with attached fibromuscular tissue and small ellipse of skin with previous biopsy scar. The specimen measured 17x9x6.5cm. Sectioning revealed a grey white solid tumor measuring 6x5cm. Representative sections from tumor along with bone and soft tissue margins were taken.

Histopathological examination revealed a biphasic tumor. There were sheets of small round blue cells containing hyperchromatic nuclei and scant cytoplasm. Mitotic figures were readily identified. Scattered in between were discrete relatively hypocellular areas composed of small round cells in a neuropil background (Figures 1B and 1C). Few ganglion cells were seen suggesting neuroblastic differentiation (Figure 1D). Immunohistochemical stain synaptophysin was positive in neuroblastomatous areas (Figure 2A), while neurofilament was negative. CD99 was positive in EWS areas (Figures 2B and 2C). Based on morphological and immunohistochemical features, a diagnosis of Ewing sarcoma/PNET with post-chemotherapy NB-like differentiation was rendered. Cytogenetic analysis of the post-chemotherapy specimen by Fluorescence *in situ* Hybridization (FISH) showed EWSR1 gene rearrangement (Figure 2D).

Postoperative bone scan and CT scan of lung showed no metastatic involvement. The postoperative chemotherapy regimen included adjunct therapy with VAC/IE and a total of 7 cycles were given post-operatively. The last cycle was given 6 months after surgery. The patient passed away, exactly 12 months after the initiation of treatment.

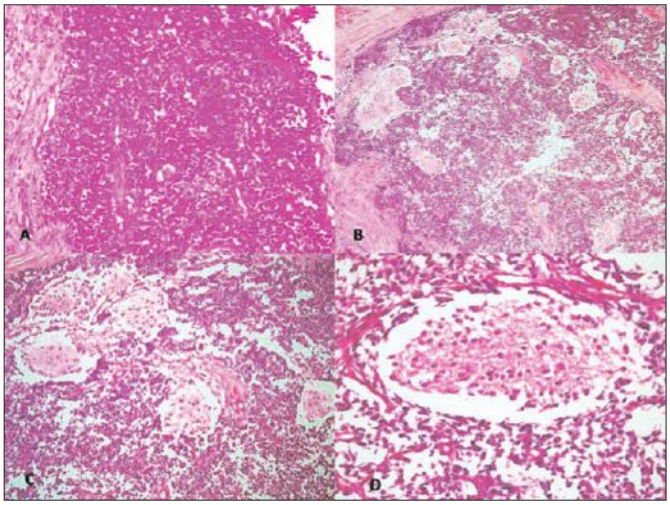

Figure 1: Pretreatment biopsy composed of sheets of round blue cells (A, H&E, 100x magnification). Posttreatment biopsy showed sheets of round blue cell with interspersed discrete hypocellular nodules in a background of neuropil (B,C; 40 & 100x magnification). Ganglionic differentiation in discrete nodules (D, H&E, 400x magnification).

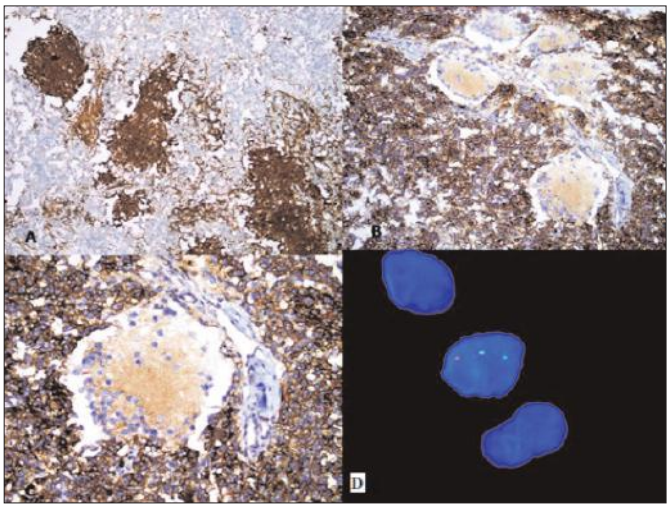

Figure 2: Synaptophysin positivity in nodules of neuroblastmatous differentiation (A). CD99 positivity in Ewing sarcoma areas with sparing of neuroblastomatous nodules (B,C). FISH for EWSR1 showed EWSR1 gene rearrangement indicated by separate green and red signals (D).

DISCUSSION

EWS/PNET may rarely exhibit evidence of complete neuronal differentiation. Such differentiation has been shown to occur spontaneously in EWS/PNETs at some peculiar sites such as cauda equina,[8] or it may become evident after treatment.[2,5-7] All cases of post-chemotherapy NB-like differentiation reported so far occurred in females between 10 to 17 years of age (mean 12.5 years).[2,5-7] Our case is the first to be reported in a male patient. Of the previous reported cases, two tumors were located in the bone (radius and iliac bone),[5,7] while two were extraskeletal (forearm and retroperitoneum).[2,6] The size of tumors ranged from 4 to 14 cms (mean 11 cms).[2,5-7] The follow-up of the reported cases ranged from 2 to 30 months (mean follow-up, 14 months).[2,5-7] One patient died of disease due to lung metastasis,[5] while the other 3 were alive at last follow-up.[2,6,7] Our patient died of disease 12 months after surgery.

It is believed that neuronal differentiation occurs in EWS patients as a result of chemotherapy.[2,5-7] The reason why chemotherapy sometimes leads to neuronal differentiation in EWS/PNET is still unclear. There is no set trend in the chemotherapy regimen or time period until surgery in the reported patients, which could be

cited as a probable common causative factor in the reported cases, as different regimens were given to these patients.[2,5-7]

All reported cases, before this one, show only one consistent trend: female gender. However, the number of reported cases is very small and there is no sufficient data to conclude that gender difference plays any role in causing neuronal differentiation following chemotherapy in patients with EWS. The possibility that neural differentiation is independent of chemotherapy cannot be entirely excluded. Recently, Vali *et al*. reported the presence of NB-like differentiation in an extraskeletal retroperitoneal EWS/PNET in the absence of any chemotherapy.[9] They hypothesized that additional genetic or epigenetic modifications may lead to the creation of a separate clone of NB-like malignant cells within the primary mass of some EWS/PNETs.[9]

The effect of neural differentiation on the prognosis of EWS/PNET is not known due to the scarcity of data available. It is possible that if more cases are reported, a new therapy regimen might be devised for the treatment of such mixed tumors. In summary, we report another example of this rare histologic change in EWS/PNET following chemotherapy highlighting the necessity of ancillary and molecular studies.

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