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Ewing Sarcoma with Ganglion Cells Post-Chemotherapy: A Case Report with Review of Literature

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Abstract

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Ewing sarcoma arises in both bones (most common) and soft tissues and it commonly affects young adults. The tumor is composed of small round cells showing positivity for CD99 and FLI1 on immunohistochemistry (IHC). We describe ganglion cell differentiation post-chemotherapy in Ewing sarcoma which is a rare phenomenon.

A 13-year-old girl presented with a chest wall mass. On biopsy correlating with IHC, the diagnosis was rendered as Ewing sarcoma. She underwent neoadjuvant chemotherapy followed by resection of the tumor. On microscopic evaluation, the tumor showed prominent ganglionic differentiation with expression of neuronal markers.

Although maturation post-chemotherapy is an established finding with better prognosis in other primitive pediatric tumors, such neural differentiation is rare with only a few case reports in Ewing sarcoma both post- and pre-chemotherapy. Clinical significance and prognosis of such differentiation which appear to be better are not yet established and needs to be elucidated.

Keywords

- Ewing sarcoma
- ganglion cell
- neural differentiation
- chemotherapy
- maturation

Introduction

Ewing sarcoma (ES) is a small blue round cell tumor that occurs in bones (most common) and soft tissues of children and young adults showing characteristic fusion usually involving EWSR1 gene. The tumor is composed of small round cells in varying pattern with fine chromatin showing positivity for CD99 and FLI1 on immunohistochemistry (IHC).[1] Neoadjuvant chemotherapy is the standard of care for patients diagnosed with ES. Post-chemotherapy, percentage of necrosis, and viable tumor cells are used as indicators of treatment response.[2] We describe a case of ES showing extensive ganglion cell differentiation post-chemotherapy which is a rare phenomenon with only a few case reports.

Materials and Methods

The biopsy and specimen slides were stained with hematoxylin and eosin stain. IHC markers used were vimentin, CD99,

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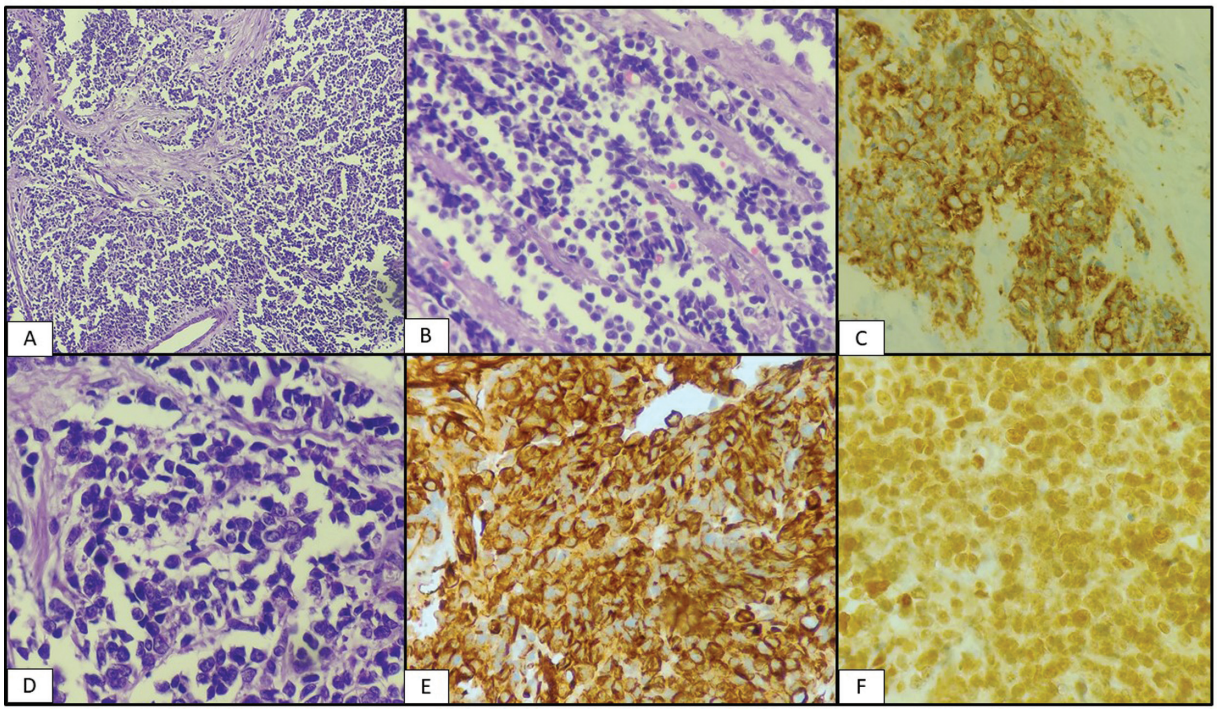

Fig. 1 Biopsy: (**A**) Tumor in nests and sheets (hematoxylin and eosin [H and E], 10x); (**B**) Filigree pattern (H and E, 40x); (**D**) Cells with prominent nucleoli (H and E, 40x); (**C**, **E**, and **F**): CD99, vimentin, and FLI1 positivity on immunohistochemistry (40x).

FLI1, synaptophysin, LCA, Tdt, desmin, and AE1. Appropriate positive and negative controls were run. Clinical details regarding the case and follow-up data were retrieved from hospital records.

Case Report

A 13-year-old female presented with dyspnea for 2 months. Computed tomography (CT) revealed an ill-defined chest wall tumor measuring $10 \times 7 \times 5\,cm^3$ with two separate pleural nodules of similar intensity, each measuring 4 and 3 cm in diameter.

Biopsy

CT-guided biopsy was done from the mass which showed a tumor infiltrating the muscle composed of small round cells in nests, trabeculae, and filigree pattern having scant cytoplasm, homogenous granular chromatin with focal pseudo rosettes (►**Fig. 1**). The cells were showing opened chromatin and prominent nucleoli in few foci. The biopsy was reported as round cell tumor with a possibility of ES. IHC was done in which the tumor cells were positive for vimentin, CD99, FLI1, focally for synaptophysin and completely negative for LCA, Tdt, desmin, and AE1 (►**Fig. 1**). Correlating with biopsy and history, a final diagnosis of atypical ES was rendered in view of opened chromatin with prominent nucleoli in few foci.

Neoadjuvant Therapy

The patient underwent three cycles of neoadjuvant chemotherapy comprising vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide following which wide local excision of chest wall was performed along with removal of pleural nodules. Post-chemotherapy CT revealed a significant reduction in the size of the mass ($6 \times 5 \times 3 cm^3$) and also the pleural nodules, each measuring 1.3 cm.

Gross Findings

The tumor was in the subcutaneous plane extending till muscular and into intercostal space, measuring $5.5 \times 5 \times 2.5$ cm^3 having ill-defined firm to soft gray white to yellowish cut surface with erosion of the ribs. The pleural nodules were soft to firm, gray-white to yellowish each measuring 1.2 and 1 cm in diameter.

Microscopy

Residual ES was identified in multiple foci with hyalinization and fibrosis (post-chemotherapy change). Also seen are diffuse sheets of ganglion cells embedded in a neuropil like background. Residual viable tumor was 9% and ganglionic differentiation was accounting to 45%. No areas of necrosis noted (0%). Both the pleural nodules showed almost exclusive population of ganglion cells (91%) with residual viable tumor accounting to 9%. On IHC, the round cell component showed diffuse, strong, and complete membranous positivity for CD99 while being focally positive for synaptophysin. The ganglion cells were diffusely positive for synaptophysin and negative for CD99 (►**Fig. 2**). Final report was given as ES with extensive ganglionic differentiation (viable tumor cells —9%, necrosis—0%, and ganglion cells—45%).

The patient is alive and event free at 8 months follow-up.

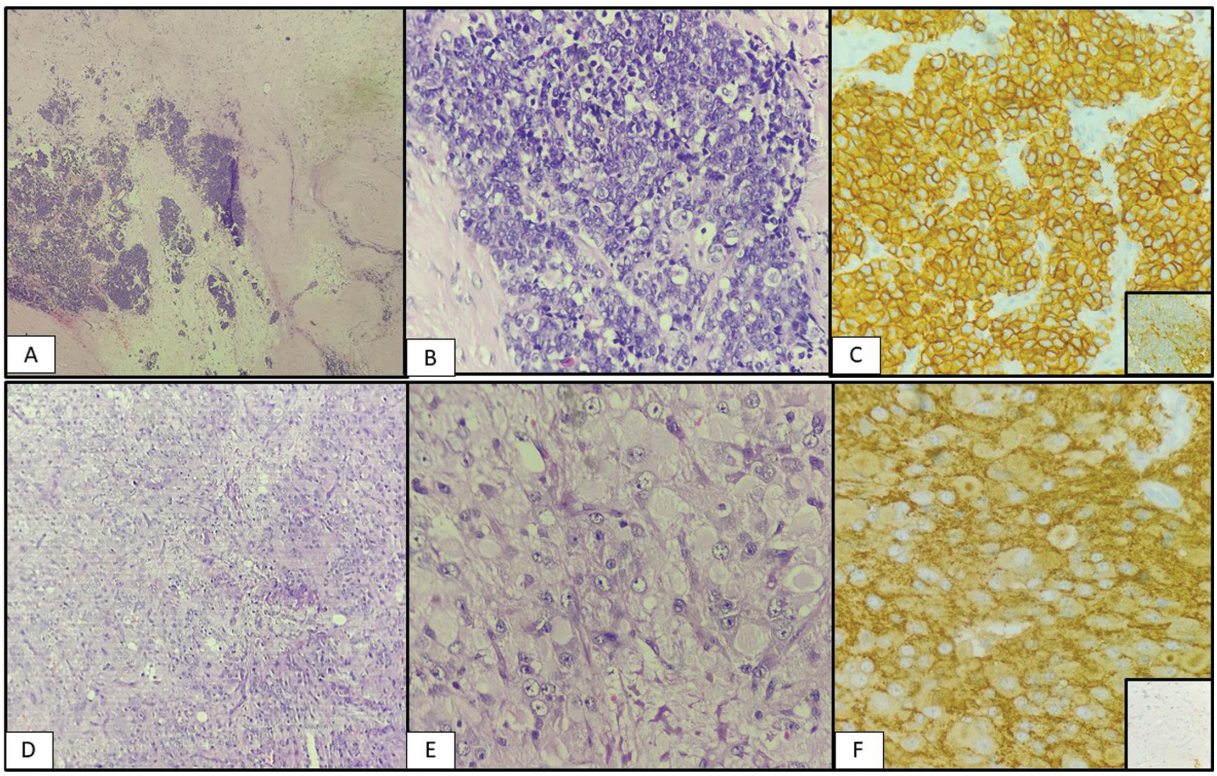

Fig. 2 Specimen: (**A**) Residual tumor (hematoxylin and eosin [H and E], 10x); (**B**) Cells with prominent nucleoli (H and E, 40x); (**C**) CD99 positivity in tumor (inset: focal synaptophysin positivity) (40x). (**D**–**F**): Ganglion cells (synaptophysin positivity in **F**) (**D**: H and E, 10x; **E**: H and E, 40x) (inset: CD99 negativity).

Discussion

Maturation and cytodifferentiation have been documented in neuroblastoma and rhabdomyosarcoma post-chemotherapy showing better prognosis[2,3]; However, this is a rare phenomenon in ES with only few case reports (►Table 1).[4–9]

In view of its histomorphology of a malignant small round cell tumor with extensive ganglion cells/neural differentiation,

Table 1 Cases of Ewing sarcoma with neural/ganglionic differentiation

Study	Age (years)/ site	Therapy status	Differentiation	Follow-up
Our case	13/chest wall	Post-chemotherapy	Ganglion cell	Event free at 8 months follow-up
Maeda et al[5]	12/radius	Post-chemo and radiotherapy	Ganglion cell	Expired at 30 months follow-up with widespread metastasis
Weissferdt et al[4]	15/lung	Pre-therapy	Ganglioneuroblastoma like	Event free at 1 year follow-up
	28/testis	Pre-therapy	Ependymoma like	Event free at 2 years follow-up
	32/cervix	Pre-therapy	Ganglioneuroblastoma like	Event free at 1 year follow-up
Erdoğan et al[6]	6/femur	Post-chemotherapy	Ganglion cell	Event free at 1 year follow-up
Salet et al[7]	8/femur	Post-chemotherapy	Ganglion cell	Event free at 21 months follow-up
Ushigome et al[9]	13/rib	Post-chemotherapy and radiotherapy	Ganglion cell	Event free at 8 years follow-up
	15/tibia	Post-chemo and radiotherapy	Ganglion cell	Expired at 2 years follow-up
	37/abdomen	Pre-therapy	Ganglion cell	Event free at 5 months follow-up
Collini et al[8]	17/iliac bone	Post-chemotherapy	Neuroblastoma like	No follow-up

the differential diagnosis of (ganglio)neuroblastoma should be considered in such cases. The later typically occurs in infants at sites having sympathetic ganglion, mostly abdomen (adrenal gland) and thoracic cavity and has more than 50% Schwannian stroma and it expresses synaptophysin, chromogranin, neuron-specific enolase) and S100 in variable proportions with consistently negative CD99. Our case, a 13-year-old female, presented with chest wall mass and was positive for CD99 (membranous—diffuse and strong); Both clinical and IHC findings rule out neuroblastoma and confirm the diagnosis of ES. Molecular confirmation may be needed in poorly differentiated small round cell tumors with conflicting immunomarker expression. However, in the present case, molecular/genetic study was not done.

ES having a (ganglio)neuroblastomatous differentiation is an unusual finding reported only rarely in literature. Maeda et al in their case report reported the first case of ES showing ganglion cell differentiation following chemotherapy and radiotherapy and they proposed two possible mechanisms to explain the appearance of ganglion cells.

1. Only those cells with the potential for neural differentiation survive, while primitive round cells are killed by the cytotoxic drugs.
2. Chemotherapeutic drugs induce active neural differentiation in tumor cells.

Both above mechanisms seem to contribute to the appearance of ganglion cells.

Multiple other studies have also highlighted the presence of ganglion cells in ES post-chemotherapy in both bones and soft tissues. To the best of our knowledge, our case is the first case of ES to show extensive ganglion cell differentiation in chest wall. In the three cases reported by Ushigome et al[9] and a single case report by Salet et al,[7] only focal ganglionic differentiation was seen, while in the single case reported by Maeda et al, the tumor was almost completely replaced by ganglion cells. The case reported by Collini et al[8] resembled neuroblastoma post-chemotherapy. In all these cases, rearrangement of EWSR1 was identified, confirming ES.

While all the case reports so far reported neural/ganglionic differentiation post-chemotherapy, Weissferdt et al reported three cases of ES with extensive neural differentiation pre-chemotherapy in unusual locations (lung, cervix, and testis) showing ganglioneuroblastoma or ependymoma like areas. Adjuvant chemotherapy was given in these cases and all the patients are alive and event free at two years post-diagnosis.[4]

ES has been proposed to arise from neural crest stem cells.[10] A possible explanation for the neural/ganglion cell/ependymomatous differentiation is the maturation of these neural crest stem cells. It has been shown from the above case reports that such neural differentiation can occur both post-chemotherapy like neuroblastoma, Wilms tumor, and rhabdomyosarcoma or as a part of primary tumor before any adjuvant therapy.[4–7]

From the limited case reports available (11 cases), neural maturation occurs both in bone and soft tissue ES, both pre- and post-neoadjuvant therapy. Important issue that needs to be addressed from all these case reports is the role of such unusual differentiation in ES and its implication in clinical behavior and outcome that appears to be better in the case reports published till date (►**Table 1**).

Conclusion

We present a case of ES showing extensive ganglion cell differentiation post-chemotherapy, which is first such case in chest wall.

Ganglion cells in ES have been documented both pre- and post-chemotherapy in ES; pathologist should be aware of such a rare phenomenon to avoid misdiagnosis

Clinical behavior and prognosis of such cases appear to be better; however, a larger study including multiple centers is required to elucidate the exact prognosis.

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Conflict of Interest
None declared.

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