Adult Primary Peripheral PNET/Ewing's Sarcoma of the Cervical and Thoracic Spine

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Abstract. *This case report describes a patient with a rare occurrence of primary spinal intramedullary Ewing's sarcoma (ES) in the cervical and thoracic spine. The older age of disease occurrence, uncommon location in the cervical and thoracic spine, and EWSR1 gene fusion as the basis of diagnosis are unique features of this case. There is no clear protocol for treatment of primary extraskeletal ES of the spine, with controversy between evidence for pursuing surgery versus a combination of radiation and chemotherapy. Our patient was treated with temozolomide chemotherapy for recurrent metastatic disease of primary ES of the spine.*

Case Report

A 44-year-old female patient initially presented in 2009 with shooting pain in her right upper extremity, which gradually progressed to involve her left upper extremity and bilateral lower extremities (BLE), leading to paraplegia and loss of sensation below the chest in the span of a few months. Spine magnetic resonance imaging (MRI) with contrast demonstrated an intramedullary enhancing lesion in the C7-T1 region, with multiple enhancing nodules distributed throughout the spine consistent with leptomeningeal dissemination. The patient underwent sub-total resection of the neurologically symptomatic cervical lesion followed by cranio-spinal irradiation (CSI) and chemotherapy involving the 'Packer regimen,' consisting of 6 cycles of cisplatin and lomustine. Pathology review of her tumor demonstrated a primary undifferentiated neuroendocrine carcinoma. Next generation sequencing (NGS) by Foundation One (Copyright) detected genomic alterations in the PIK3 pathway (PIK3CA Q546R – subclonal) and *EWSR1-FLII* fusion (*IGF-1* mutation). Her enhancing lesions disappeared

after the initial treatment regimen. Follow-up imaging in August 2012 revealed a discrete recurrent lumbar metastasis behind the L4 vertebra, and she received Cyberknife stereotactic radiosurgery (SRS) followed by ICE (ifosfamide, carboplatin, etoposide) chemotherapy for 5 of 6 planned cycles; due to chemotherapy side effects she did not complete the 6th cycle. The patient was stable and apparently disease-free until August 2016, when she presented with worsening gait, multiple falls, and BLE weakness. MRI of the spine showed recurrence of another discrete lumbar metastasis behind L2, which was treated again with Cyberknife SRS. She developed multiple leptomeningeal recurrent tumor nodules in July of 2017, and was treated with 3 months of Afinitor 10 mg daily through December 2017. She progressed on Afinitor and was treated with 8 cycles of monthly temozolomide at 200 mg/m²/day ×5 every 28 days. She had progression again in August of 2018, and is receiving carboplatin at an AUC of 4 every 4 weeks with bevacizumab 10 mg/kg every 2 weeks. She is tolerating this treatment regimen well and had a partial tumor response. She has received 7 cycles to date and is currently radiographically and clinically stable.

Discussion

The Ewing's sarcoma family of tumors (ESFT) is most commonly comprised of primary Ewing's sarcoma (ES) of the bone, but also includes extraskeletal ES, peripheral primitive neuroectodermal tumor (pPNET), and Askin tumor (thoracopulmonary PNET) (1). ES is primarily a childhood and adolescent malignancy, with peak incidence in the second decade of life (2), and belongs to the subset of PNETs (3). While the majority of ESFT are primary bone tumors, soft tissue can also be involved, most commonly at the paravertebral region and less so at the epidural space (4). In contrast, intradural involvement by CNS-PNETs (Central nervous system PNET) is exceedingly rare (5).

From 1978-2011, there have been 29 reported cases of primary spinal intramedullary CNS-PNETs across 22 case reports (6-8). Among these 29 cases, the average age of occurrence of primary spinal ES was 19 (ranges from ages

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6-32) (8). Our patient's age of 44 years old at time of tumor diagnosis falls considerably outside the upper end of this range.

Ewing's sarcoma and related pPNETs have been demonstrated to share a recurrent chromosomal translocation, t(11;22)(q24;q12), which fuses a portion of the *EWSR1* gene on chromosome 22 to a portion of the *FLII* gene on chromosome 11 (9). The *EWS* gene codes for a highly conserved RNA binding protein containing an RNA recognition motif, allowing for interaction with RNA or single-stranded DNA (10). The *FLII* gene codes for the FLI protein, which belongs to the ETS (erythroblastosis virus-transforming sequence) oncogene family and mediates cellular development and oncogenesis (11, 12). The ETS domain, constituted by a highly conserved 85-amino acid domain, allows for specific binding to DNA sequences (13). As a result of the *EWSR1-FLII* gene translocation, the expressed fusion protein is able to bind DNA *via* the ETS domain and control gene expression *via* the RNA-binding properties of the EWS protein. Approximately 85-90% of ESFTs are characterized by this t(11;22) *ESWR1-FLII* translocation (14).

Our patients' tumor had genomic alterations in the PIK3CA pathway as well as *IGF-1* with an *EWSR1-FLII* fusion. There has been one other case documented to have an *ESWR1* gene rearrangement as the histopathologic foundation for the diagnosis of primary epidural ES (15). The reported incidence of primary intraspinal ES or pPNET is twice as high in the lumbar region as the cervical or thoracic region, making the location of this tumor in the C7-T1 region even more uncommon (8). Our case is the first reported female patient with cervical and thoracic involvement with the diagnosis confirmed by the presence of the *ESWR1* gene fusion using immunohistochemistry.

Due to the limited number of reported patient cases, primary ES affecting the spine has no definite treatment protocol, though *en bloc* resection with safe margins, if possible, is currently regarded as the most important initial prognostic intervention (15, 16). Kinsella *et al.* have reported that the combination of chemotherapy and radiotherapy is more important for management than surgery, especially given the difficulty of achieving a gross total resection in these patients (17, 18). The decision to pursue surgery, even in cases of spinal cord compression from ES, is controversial. Mirzaei *et al.* performed a retrospective study of fifteen patients with primary ES of the spine and found that chemotherapy can be effective as an initial treatment option even in cases of severe spinal cord compression (19).

Conclusion

In conclusion, to the best of our knowledge, this is the only reported case of recurrent metastatic primary ES of the cervical spine, where temozolomide was used as part of the

treatment. Although the patient subsequently progressed, she was able to achieve at least eight months of progression-free survival on temozolomide. All such rare tumors that involve the CNS should be analyzed by NGS in order to better characterize and understand their behavior and ultimately determine their most effective treatments.

Conflicts of Interest

Dr. Emmanuel Mantilla's fellowship was partially funded by an educational grant from AbbVie pharmaceuticals. There are no other conflicts of interest to report.

Authors' Contributions

Raamis Khwaja: Primary author of manuscript, helped conduct literature review and wrote the abstract, case report, discussion, and conclusions sections of the paper; Emmanuel Mantilla: Helped conduct literature review, wrote and edited portions of case report, discussion and conclusion sections of paper; Karen Fink: Contributed clinical data, reviewed and edited case report and discussion; Edward Pan: Senior author of manuscript, contributed clinical data, edited the case report, discussion and conclusion sections of paper, oversaw research conduct.

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