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Spinal ependymoma, MYCN-amplified with multiple extra-CNS metastases

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Case Report

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Abstract

Spinal ependymoma, *MYCN*-amplified was first recognized in the 5th edition of the WHO Classification of Tumors as a clinically aggressive entity with high-grade histologic features, frequent recurrence, and cerebrospinal fluid dissemination. Extra-central nervous system (CNS) metastasis is exceptionally rare in ependymoma, emerging years after resection of the intracranial or spinal primary, and has not yet been described in spinal ependymoma, *MYCN*-amplified. Herein, we describe a 68-year-old man who presented with urinary retention and paraplegia. MRI revealed a T2-3 intradural extramedullary solid and cystic enhancing mass with intramedullary extension and confluent subarachnoid drop metastases at lower spinal levels. He underwent subtotal resection followed by a negative cerebrospinal fluid (CSF) cytology at postoperative week three. The histopathological diagnosis was spinal ependymoma, CNS WHO grade 3. Next-generation sequencing (NGS) identified *MYCN* amplification. The patient received adjuvant craniospinal irradiation. At one year, leptomeningeal disease was stable, but the follow-up imaging identified a right paraspinal soft tissue mass. At three years, he presented with a fall and was found to have a nondisplaced pathologic right femoral neck fracture through a lytic lesion. Staging imaging revealed multiple pulmonary and hilar masses, perihilar masses, and mediastinal and hilar lymphadenopathy, without intracranial disease. Fine-needle aspiration (FNA) and endobronchial biopsy of hilar lymph nodes were performed, along with resection of the proximal femoral mass. Histopathologic examination and fluorescence in situ hybridization of the thoracic lymph node and femoral biopsies showed metastatic grade 3 *MYCN*-amplified ependymoma morphologically consistent with the primary tumor, which was confirmed with methylation and copy number profiling. He underwent long-stem hip hemiarthroplasty with prophylactic femoral fixation, followed by radiation therapy to the femur and systemic temozolomide and lapatinib. This case expands the spectrum of clinical behavior and molecular pathological understanding of this recently defined entity.

Introduction

Spinal ependymoma, *MYCN*-amplified (SP-EPN-MYCN) is a clinically aggressive entity, first recognized in the 2021 5th edition of the WHO Classification of Central Nervous System Tumors. Prior to this edition, spinal ependymomas were classified into three entities: subependymoma, myxopapillary ependymoma, and spinal ependymoma (classical). Between 2019 and 2020, several studies identified a subset of spinal ependymomas harboring *MYCN* amplification with particularly aggressive clinical behavior and a distinct DNA methylation profile (Swanson et al., 7 cases; Ghasemi et al., 13 cases; Raffeld et al., 7 cases) [6, 13, 15]. These tumors demonstrated high *MYCN* copy number and concurrent chromosomal copy number alterations but notably lacked the *NF2* loss (or chromosome 22q loss) that characterizes approximately 90% of classical spinal ependymomas. Despite high-intensity treatment, SP-EPN-MYCN showed significantly worse outcomes compared to all other spinal ependymoma subgroups, with a median progression-free survival (PFS) of 17 months and median overall survival (OS) of 87 months. Accordingly, this entity was proposed as a distinct subclass of spinal ependymoma in cIMPACT-NOW Update 7 [3], and it was subsequently incorporated into the WHO CNS tumor classification, 5th edition [8]. Since then, retrospective studies applying the updated classification have revealed that SP-EPN-

MYCN comprises approximately 6–10% of spinal ependymomas overall, and up to 25% of grade 3 spinal ependymomas [12, 14].

Histologically, SP-EPN-MYCN shares features with other grade 3 ependymomas, including hypercellularity, marked cytological atypia, prominent nucleoli, geographic necrosis, glomeruloid microvascular proliferation, and increased mitotic activity [13]. Immunohistochemically, these tumors are positive for GFAP and demonstrate dot-like perinuclear EMA staining, with Ki-67 proliferation indices ranging from 3% to 60% [6, 14]. True ependymal rosettes are characteristically absent, but cystic components within the tumor have been reported in a subset of cases [13]. *MYCN* copy number by NGS has ranged from 11 to 170 [13] and has been suggested to correlate with Ki-67 proliferation index [6]. MYCN immunohistochemistry, when available, is useful as a screening tool for *MYCN* amplification.

MYCN amplification is considered the primary oncogenic driver in this entity. Additional genetic alterations are variable and include multiple concurrent chromosomal copy number changes. Loss of chromosome 10 and gain of chromosome 18 (Supplemental Figure S1) have been reported across multiple cases and studies [6, 15]. Gains of chromosomal segments involving *PIK3C2B* and *NF1* [15], as well as *YAP1* and *BRD4* [6], and losses involving *NBAS, DNMT3A*, and *TP53*, along with variants of unknown significance in *NOTCH1, KMT2D, PLCG1*, and *POLE* [15], have also been reported at the individual case level. Unlike classical spinal ependymoma, loss of chromosome 22q (*NF2* locus) has not been described. Similarly, loss of chromosome 6 and *CDKN2A/B* deletions, which are common in posterior fossa and supratentorial ependymoma, respectively, have not been observed in this entity [2, 7].

These studies uniformly describe frequent CNS dissemination, both at initial diagnosis and during the clinical course, with significantly worse PFS and OS compared to *MYCN*-wildtype spinal ependymomas. The clinical outcomes are comparable to, or even worse than, those of posterior fossa type A ependymoma and supratentorial ependymoma with *RELA* fusion. Extra-CNS metastasis has been reported as a rare event predominantly in supratentorial ependymomas [5, 11], but to our knowledge has not been previously reported in SP-EPN-MYCN, despite matching or worse survival outcomes. Herein, we report a case of SP-EPN-MYCN with extra-CNS metastases to hilar lymph nodes and the femoral neck.

Case Report

The initial presentation and treatment of this case was previously published in Ezzat et al [4]. A 68-year-old man with a history of occupational exposure at the World Trade Center site for approximately two years following September 11, 2001 (Supplementary Note S3) presented with urinary retention and paraplegia. Spinal MRI revealed a T2-3 intradural extramedullary solid and cystic enhancing mass with confluent subarachnoid drop metastases at lower spinal levels (Fig. 1A) [4]. He underwent a T2-3 laminectomy with near total resection followed by adjuvant proton craniospinal irradiation. Intraoperatively, the mass was described as a soft, fleshy, gray-and-yellow lesion adherent to thickened spinal dura, with cystic and solid components. A portion of tumor was densely adherent to the spinal

cord itself, and gross total resection was not achieved due to concern for cord injury. Postoperative cerebrospinal fluid (CSF) cytology at three weeks was negative for malignancy.

Microscopic examination of the resection specimen revealed a poorly differentiated neoplasm composed of relatively monomorphic round to polygonal cells with hyperchromatic nuclei and high nuclear-to-cytoplasmic ratio, without distinct rosette formation (Fig. 2A). By immunohistochemistry, the tumor was diffusely positive for GFAP, negative for OLIG2, and showed focal perinuclear dot-like staining with EMA. The Ki-67 proliferation index was > 50% (Fig. 2B). The morphology and immunophenotype were most compatible with spinal ependymoma, CNS WHO grade 3. Comprehensive genomic profiling of the primary tumor was performed using FoundationOne CDx (Foundation Medicine, Cambridge, MA), which identified *MYCN* amplification with additional variants of uncertain significance (Table 1). Interphase fluorescence in situ hybridization (FISH) confirmed *MYCN* amplification in 97% of tumor cells (Fig. 2C). The diagnosis of SP-EPN-MYCN was rendered. The patient received proton beam craniospinal irradiation after the surgery to treat the leptomeningeal disease. Following radiation, his brain and spine MRIs remained stable without evidence of progression for approximately 1.5 years, but a right paraspinal soft tissue mass was identified at the end of this interval. In the meantime, the patient continued rehabilitation and improved from wheelchair-bound status to walking independently without an assistive device. Ezzat et al. described the unusual intradural extramedullary location and favorable response to radiotherapy after the first resection [4]. Notably, the patient already had leptomeningeal disease at the time of initial diagnosis, a finding that would often preclude surgical intervention due to expected poor prognosis; however, he responded well to surgery and adjuvant radiation before developing the extra-CNS metastatic disease described below.

Table 1
Summary of next-generation sequencing findings (FoundationOne CDx).

Amplifications:
- *MYCN* (2p24)
- *RICTOR* (5p13) (equivocal)
- *FGF10* (5p12) (equivocal)
Loss:
- *KEL* (7q34) loss
Variants of uncertain significance:
- Amplification: *APC*(5q22), *BCL2*(18q21), *CSF1R*(5q32), *CTNNA1*(5q31), *FGFR4*(5q35), *GABRA6*(5q34), *GATA6*(18q11), *MAP3K1*(5q11), *MSH3*(5q14), *NOTCH1*(9q34), *NPM1*(5q35), *PDGFRB*(5q32), *PIK3R1*(5q13), *SDHA*(5p15), *SMAD2*(18q21), *SMAD4*(18q21), *SNCAIP*(5q23)
- Mutations: *HNF1A*, *KEL*, *NT5C*, *PIK3C2G*, *PTCH1*, *RB1*
Genomic signature:
- Microsatellite stable
- Tumor Mutational Burden = 0 mutations/Mb

Thirty-three months after the surgery, the patient presented after a fall. An MRI of the right femur demonstrated a nondisplaced pathologic femoral neck fracture overlying a mass together with a large osseous lesion in the right iliac bone adjacent to the sacroiliac joint (Fig. 1B). Staging imaging revealed previously unrecognized extra-CNS disease comprising a 4.3 cm right perihilar mass (Fig. 1C), a 2.3 cm right upper lobe nodule, a 2.8 cm left hilar nodule (Fig. 1D), extensive bilateral hilar and mediastinal lymphadenopathy, and numerous smaller bilateral pulmonary nodules, with no radiographic evidence of intracranial metastasis. Fine-needle aspiration (FNA) and endobronchial biopsy of masses at the hilar lymph nodes (11Ri and 11L) were performed. Microscopic sections of 11Ri revealed a poorly differentiated neoplasm morphologically consistent with the primary spinal ependymoma with > 90% Ki-67 (Fig. 2D-E). FISH demonstrated high-level *MYCN* amplification in more than 97% of tumor cells (Fig. 2F), confirming the diagnosis of metastatic SP-EPN-MYCN. The FNA specimen of 11L showed clusters of cells with high nuclear-to-cytoplasmic ratio and hyperchromatic nuclei. GFAP immunostaining on a cell block was positive (Fig. 2G).

The patient subsequently underwent biopsy and resection of the proximal femoral tumor with long-stem hip hemiarthroplasty and prophylactic femoral fixation (Fig. 1E), and histopathology showed tumor consistent with metastatic ependymoma infiltrating within bone trabeculae (Fig. 2H-I). Adjuvant photon radiation therapy to the right femur was completed over six fractions, after which systemic therapy with temozolomide (125 mg/m² on days 1–7 and 15–21 of a 28-day cycle) and lapatinib (1250 mg daily) was initiated. At follow-up, the patient remained clinically stable and ambulatory with only mild treatment-related cytopenias that did not require dose reduction, and serial brain and spine MRI demonstrated

stable thoracic and lumbar subarachnoid disease, stable systemic disease, and no intracranial metastasis, but an increased number of extra-CNS regions with avid FDG uptake was seen on positron emission tomography-computed tomography (PET-CT), including a right paraspinal soft tissue mass, right iliac bone, left humerus, and bilateral ribs.

Methylation and copy number profiling were performed on the initial T2-3 spinal tumor and the 11Ri lymph node. The initial T2-3 spinal tumor matched to the methylation subclass EPN-SPINE-MYCN with a Bethesda Classifier v3.1 confidence score of 0.982, and the 11Ri lymph node matched with a confidence score of 0.984 (Supplemental Figure S2). Copy number profiling demonstrated similar copy number alterations in both the primary and metastatic lesion, including *MYCN* amplification and gain of chromosome 5 and 18 (Fig. 2J-K).

Discussion

Extra-CNS metastasis is a rare but recognized phenomenon in ependymomas, reported predominantly in supratentorial and myxopapillary ependymomas [5, 11]. Reported metastatic sites include lymph nodes, lung, bone, parotid gland, and scalp [11, 16]. The potential mechanisms of extra-CNS spread include hematogenous dissemination, lymphatic spread, and iatrogenic seeding along the surgical tract [11]. Given that SP-EPN-MYCN demonstrates OS and PFS comparable to or worse than supratentorial ependymomas, combined with a remarkably high frequency of CNS dissemination, it is perhaps not surprising that extra-CNS metastasis can also occur in this entity. However, why this occurred in the present case and not in previously reported cases remains unclear.

Notably, this patient's clinical course was not remarkable for unusually aggressive behavior compared to published cases of SP-EPN-MYCN specifically. The PFS of approximately 6 months (leptomeningeal progression after subtotal resection) and OS of at least 36 months fall within the expected range for this entity (median PFS 17 months, median OS 87 months) [6, 15]. Furthermore, although extra-CNS metastases developed, the leptomeningeal disease remained radiologically stable from 6 months post-surgery onward, and no brain parenchymal metastases were observed. Thus, this case cannot be characterized as an outlier in terms of overall clinical aggressiveness. Histologically, the present case showed a poorly differentiated appearance, and the Ki-67 proliferation index of 60% was at the upper end of the reported range [6]. This elevated Ki-67 may suggest a correspondingly high *MYCN* copy number; however, whether the degree of *MYCN* amplification is associated with extra-CNS metastatic potential, or with PFS and OS more broadly, cannot be determined from a single case.

Next generation sequencing (NGS) and DNA methylation profiling revealed additional genetic alterations beyond *MYCN* amplification (Table 1). These included loss of *KEL* and gains of multiple genes on chromosomes 5 and 18 resulting from gain of these chromosomes, among which *RICTOR* (located on 5p13) and *FGF10* (located on 5p12) might be pathogenically significant, though detected only at an equivocal level. *RICTOR* overexpression has been associated with transforming capability [18], and as a component of the mTORC2 complex, *RICTOR* has been implicated in cancer cell migration and

metastasis. *FGF10* expression in various cancer models induces cellular proliferation, migration, and invasion, suggesting a predominantly oncogenic function [1, 10]. These chromosomal copy number changes are consistent with the multiple concurrent chromosomal arm-level alterations previously described in SP-EPN-MYCN [6, 13, 15]. Gain of chromosomes 5 and 18 specifically has been reported in Swanson's cases 2 and 3 and in two cases from Ghasemi's cohort, suggesting these may be recurrent findings in a subset of this entity [6, 15]. Whether these alterations, particularly gain of *RICTOR* and *FGF10*, given their established oncogenic mechanisms, contributed to the metastatic potential in this case warrants further investigation as additional cases are characterized.

Clinically, this case raises several considerations worth documenting for future reference. Surveillance at follow-up should not be limited to craniospinal MRI and cerebrospinal fluid analysis but should also include systemic imaging to evaluate for extra-CNS disease. Management of skeletal metastasis is necessarily multidisciplinary and combines orthopedic stabilization, local radiation, and systemic therapy, since the immediate threat to function is mechanical as much as oncologic. The present case underwent resection of the femoral tumor with long-stem hip hemiarthroplasty and prophylactic fixation, which restored ambulation, followed by photon radiation to the femur and systemic temozolomide and lapatinib, an approach consistent with the surgery, radiation, and chemotherapy combinations used in prior extra-CNS series even though durable control of disseminated ependymoma, particularly this molecularly distinct subtype, remains elusive [9, 16, 17]. Preservation of ambulation and reliable pain control are realistic and worthwhile goals when cure is not attainable. As additional cases accumulate, treatment strategies directed at extra-CNS metastatic sites will need to be developed and evaluated.

Conclusion

This is the first reported case of SP-EPN-MYCN with distant extra-CNS metastases, involving hilar lymph nodes and bone. The principal lesson is that this entity, already recognized for its high frequency of CNS dissemination, can also give rise to extra-CNS metastases, even in patients whose clinical course is not exceptionally prolonged or aggressive. Whether the poorly differentiated histology with an extremely high Ki-67 proliferation index (60%), a high *MYCN* copy number, and additional chromosomal copy number alterations, particularly gain of chromosome 5 involving *RICTOR* and *FGF10*, have contributed to this behavior merits further investigation. The lesson learned from managing this challenging case underscores the importance of multidisciplinary care and informs the design of future prospective studies for this recently defined tumor type.

Abbreviations

- **CNS**
Central Nervous System
- **CSF**
Cerebrospinal Fluid
- **EMA**

Epithelial Membrane Antigen
• **FISH**
Fluorescence In Situ Hybridization
• **FNA**
Fine–Needle Aspiration
• **GFAP**
Glial Fibrillary Acidic Protein
• **MRI**
Magnetic Resonance Imaging
• **NGS**
Next–Generation Sequencing
• **OS**
Overall Survival
• **PFS**
Progression–Free Survival
• **SP**
EPN–**MYCN**–Spinal Ependymoma, MYCN–amplified
• **WHO**
World Health Organization
• **cIMPACT**
NOW–The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy–Not Official WHO

Declarations

Ethics approval and consent to participate:

Formal ethics approval was not required for this case report, in accordance with institutional policies.

Consent for publication:

Written informed consent for publication of this case report and any accompanying images or other identifiable information was obtained from the patient.

Competing interests:

TER has received consulting fees from Servier Pharmaceuticals, which is unrelated to the current work. The results presented in this paper have not been published previously.

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Author Contribution

Authors' contributions: SH, BE, TER, and AB contributed to the study conception and design. SH, BE, MCV, TY, MS, EG, JT, GKH, NMT, MBB, KE, SL, TER, and AB, contributed materials, data collection, and performed pathologic analysis. ZA and OS performed methylation profiling. SL performed radiologic analysis. All authors have reviewed and approved the final manuscript.

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Availability of data and material:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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