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Case Report

Papillary Thyroid Carcinoma-Like Tumor with *BRAF* Fusion in Spine Responds to Trametinib Chemotherapy

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Abstract

Spinal tumors are rare in pediatric patients. Papillary thyroid carcinoma is equally rare. Here we report an exceptional pediatric case of papillary thyroid carcinoma-like tumor with *BRAF* fusion, spinal primary type and highlight the tumor response to Trametinib chemotherapy. We discuss the multidisciplinary management of this case along with literature review.

Keywords: Spinal; Papillary; Thyroid; Carcinoma; Trametinib

Abbreviations

CNS: Central Nervous System; MRI: Magnetic Resonance Imaging; PTC: Papillary Thyroid Carcinoma; T: Thoracic; L: Lumbar; PET: Positron Emission Tomography; CT: Computed Tomography; SUV: Standardized Uptake Value; ENT: Ear Nose Throat; MEK, MAPK: Mitogen-Activated Protein Kinase

Introduction

Central Nervous System (CNS) tumors are the most common solid tumors in the pediatric age group in USA, accounting for around 15% of pediatric cancers. Spinal cord tumors comprise around 5-10% of pediatric CNS tumors [1]. These tumors originate more commonly from intramedullary (~50%) and less commonly from the extradural (~30%) or extramedullary intradural (~20%) compartments. The most common presentation of these tumors is back pain followed by neurological deficit [2]. Nocturnal or persistent back pain must prompt comprehensive evaluation including Magnetic Resonance Imaging (MRI) of full spine [3].

Papillary Thyroid Carcinoma (PTC) is a differentiated type of thyroid cancer accounting for approximately 5% of pediatric cancer cases. The incidence of PTC has been on a rise and increases with age [4]. Here we report an exceptional pediatric case of PTC-like tumor with *BRAF* fusion, spinal primary type and highlight tumor response to Trametinib chemotherapy. We discuss the multidisciplinary management of this case along with literature review.

Case Presentation

A 6-years-old girl presented with symptoms of bilateral thigh and hip pain lasting more than a year. Her pain progressively worsened causing nocturnal waking and school absence. Rheumatologic and orthopedic workup came back negative. Eventually, the patient developed left foot drag and suffered from frequent falls and urinary and fecal incontinence prompting an urgent referral to pediatric neurology. MRI of the brain was normal. MRI of full spine revealed a well-defined, enhancing, lobulated Thoracic (T)-12 to Lumbar (L)-1 mass, 3.6cm craniocaudal by 2.4cm transverse by 1.8cm antero-posterior, occupying the entire circumference of the spinal canal, causing expansion of canal, mild remodeling of T12 and T11 vertebral bodies and obscuring distal cord with substantial cord edema extending up to T8-9 level. It was noted to be poorly compartmentalized between intramedullary or intradural extramedullary sites.

Neurosurgical debulking involved T12-L2 laminectomies for resection of mass with intraoperative neuromonitoring. The intramedullary tumor was centered at T12 and L1 and had fleshy gray to tan color. It was centrally debulked at the inferior border and then dorsally. Post-operative MRI spine confirmed residual tumor in ventral and superior sites. After surgical recovery, the patient experienced prompt resolution of frequent falling, urinary and fecal incontinence, no longer complained of hip or thigh pain and could sleep through the night and wake up pain-free, and displayed stable left foot drag.

Neuropathology of the tumor revealed a well-differentiated papillary tumor with nuclear features (pseudo-inclusions and nuclear crowding) resembling those of papillary thyroid carcinoma. Extensive immunohistochemical testing (diffuse and strong nuclear staining for TTF-1, positive for PAX8, CK7, CAM5.2, pancytokeratin, focally positive for thyroglobulin & S-100 and negative for EMA, PR, GFAP, synaptophysin, PLAP, AFP, D240 and CD99) was compatible with thyroid phenotype. Mitotic activity was low. Cytogenetic evaluation of the tumor revealed *BRAF-KIAA1549* fusion.

Comprehensive multi-disciplinary workup was initiated to categorize this spinal tumor as metastatic versus ectopic versus spinal primary. On clinical exam, the endocrinologist did not detect any thyromegaly or prominence of thyroid gland or palpable nodules or palpable lymph nodes or pubertal changes. Endocrine workup showed no evidence of autoimmune thyroiditis or hypothyroidism or hyperthyroidism. Thyroglobulin was detectable, as expected with an intact, functioning thyroid gland. Neck ultrasound was negative for thyroid nodules or cervical lymphadenopathy. Nuclear medicine Iodine-123 whole body scan showed normal physiologic tracer uptake

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Table 1: Literature review of primary spinal PTC cases.

Author, publication date	Patient age, gender at diagnosis	Location & features of spinal PTC	Therapies	Outcome
Consencino EPD et al., 2011	17 y/o female	T3-T4 intramedullary nodule, PTC	Surgical excision of spinal tumor, total thyroidectomy, avoided radioactive ablation, thyrotropin suppression	Alive at 2 years' post diagnosis, remains paraplegic
Han S et al., 2020	69 y/o female	T6-T7 epidural mass, follicular variant PTC, normal thyroid follicles near mass	Surgical excision, h/o partial thyroidectomy, no further thyroid exploration done with current diagnosis	Recurrent tumor 1 year post diagnosis, patient refused therapy
Current report	6 y/o female	T12-L1 intramedullary mass, PTC-like tumor with *BRAF* fusion	Excision of spinal tumor, targeted chemotherapy with MEK inhibitor	Alive at 3 years' post diagnosis, on chemotherapy

y/o: years old; T: Thoracic; L: Lumbar; PTC: Papillary Thyroid Carcinoma; MEK: Mitogen Activated Protein Kinase.

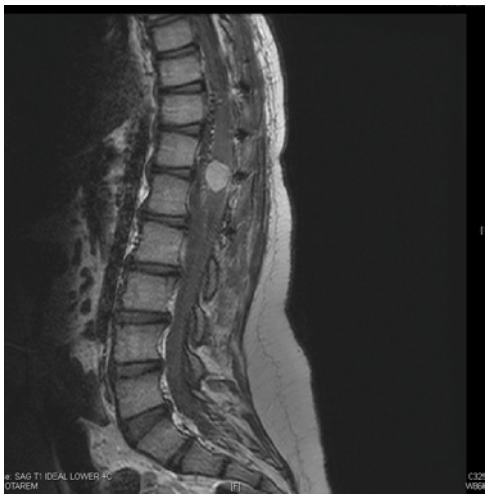

Figure 1: MRI spine with and without contrast showing intramedullary spinal PTC-like tumor pre-chemotherapy.

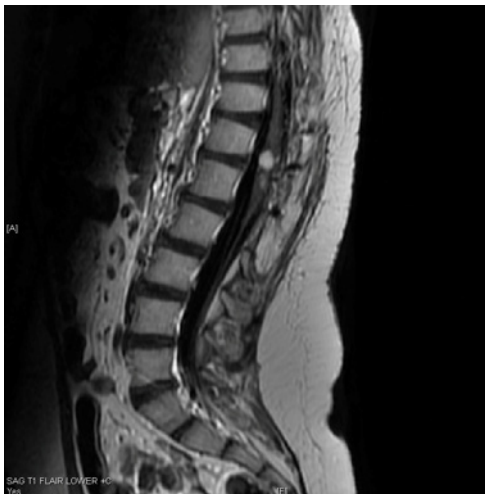

Figure 2: MRI spine with and without contrast showing intramedullary spinal PTC-like tumor 30 months on chemotherapy.

in thyroid gland and no abnormal tracer activity in spinal canal. Positron Emission Tomography (PET) computed tomography (CT) whole body scan showed increased uptake within left lobe of thyroid gland (SUV 10.8), mild uptake in paraspinal region corresponding to the surgical site but no uptake was noted at the spinal residual tumor site. Ultrasound of the ovaries did not show evidence of struma ovarii. Overall, endocrine workup did not reveal evidence of a thyroid metastasis.

Total thyroidectomy was planned to rule out microscopic thyroid carcinoma, potential need to use I-131 therapy and to use thyroglobulin as a marker for the residual spinal tumor. Accordingly, the ENT surgeon performed total thyroidectomy with resection of a pyramidal lobe uneventfully. Thyroid histopathology showed rare follicles with intraluminal foamy macrophages, multinucleated giant cells, and foci of dystrophic calcification consistent with palpation thyroiditis. No malignancy was identified. Post thyroidectomy, the patient was started on thyroid supplement. Nuclear medicine Iodine-123 whole body scan showed uptake only in the neck, concerning for residual thyroid tissue and for a metastatic node but no spinal canal uptake was noted. PET-CT whole body scan confirmed residual thyroid tissue (SUV max 7.6) without any metastatic node and showed interval increased uptake in spinal canal residual mass (SUV max 3.9). MRI full spine showed stable size of residual enhancing tumor (Figure 1).

Based on this extensive workup, the residual spinal tumor was categorized as a PTC-like tumor, spinal primary type. Thyroid supplement was transitioned to levothyroxine therapy with target of TSH <0.1mIU/mL based on American Thyroid Association Task for On Pediatric Thyroid Cancer guidelines [5]. Extensive discussion was carried out with the family regarding adjuvant therapy for residual spinal tumor. External beam radiation therapy option was discussed but its utility in controlling the residual tumor was deemed low, also the patient's young age precluded its use prior to spinal maturity. Chemotherapy option with MEK (Mitogen activated protein kinase) inhibitor Trametinib was offered due to this tumor harboring *BRAF-KIAA1549* fusion and was accepted by the family.

Patient was started on Trametinib at 0.025mg per kg per day orally. Close clinical and laboratory monitoring showed expected side effects of mucositis, paronychia and fever. About 3 months into this therapy, as the adverse effects became intolerable (grade II) affecting patient's quality of life, Trametinib was held for a week then restarted at 10% lower dose. Around 6 months into this therapy, the patient also developed patchy alopecia and arthralgia, prompting another hold of chemotherapy for 2 weeks which led to prompt improvement in symptoms, then chemotherapy was resumed at a further lower dose. During this time frame, MRI spine showed partial tumor response with 30% reduction in spinal tumor volume, which was quite encouraging despite of the sub-therapeutic dosing. Around a year on Trametinib, patient experienced exponential constitutional growth consistent with familial growth pattern, prompting Trametinib dose increase by 10%. Patient currently remains on this dose without any compromise in quality of life and at fully functional state. The

latest MRI spine performed 30 months on Trametinib chemotherapy demonstrated 65% reduction in the tumor volume (Figure 2).

Discussion

PTC-like tumor with spinal primary is an extremely unusual diagnosis. This is the 3rd case reported world-wide and the only pediatric case reported from USA (Table 1). The unique characteristic of this case is the young age at diagnosis (compared to the previous pediatric case), the detection of *BRAF* fusion (instead of *BRAFv600E* mutation) and the sustained response of the residual tumor to low dose Trametinib [6,7].

Of note, *BRAFv600E* mutations have been described in around 50% of PTC but *BRAF* fusion is found less commonly, enriching only 3% of PTC [8,9]. Trametinib, a MEK inhibitor, has shown promising tumor control in pediatric low-grade gliomas as MAPK pathway is predominant in these tumors and *BRAF-KIAA1549* fusion is found in 80% of pilocytic astrocytomas [10-12]. Use of MEK inhibitor as a stand-alone chemotherapy for adult-onset PTC [13,14] as well as its use in combination with *BRAF* inhibitors has been well described [13] but its use in pediatric-onset PTC has not been described so far, let alone in pediatric PTC-like tumor with spinal primary [4,15]. Additionally, with regards to further therapeutic options, I-131 radio ablation may deserve future consideration as ongoing clinical trials involving *BRAF* inhibitors and MEK inhibitors to treat thyroid cancer suggest there may be effect on iodine avidity in previously iodine resistant PTC [13,14].

In summary, this case report highlights the diagnostic challenges posed by an exceptionally rare pediatric tumor and reinforces the need to provide extensive multidisciplinary care for optimum clinical outcome. It also brings into focus the importance of genetic workup for rare diseases and the promising result that targeted therapy can provide, even when applied to an exceptional case as this.

Acknowledgement

Written informed consent for publication of the clinical details was obtained from the parent of the patient. A copy of the consent form is available for review by the Editor of this journal.

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