

Multiple Metastatic Somatic Tissue Ganglioneuroma from a Primary Adrenal Ganglioneuroblastoma in a Pediatric Patient

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Citation: Eden Story and Donna Johnston (2016) Multiple Metastatic Somatic Tissue Ganglioneuroma from a Primary Adrenal Ganglioneuroblastoma in a Pediatric Patient. *Cancer Res Oncol* 2: 005.

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Abstract

Neuroblastic tumors are classified based on age and histological appearance. They fall along a spectrum of tumor maturity, which dictates tumor aggression and course. Ganglioneuromas and intermixed ganglioneuroblastomas are the most mature subtypes that tend to present with unifocal disease and have a benign course. We present a unique case of a 3-year-old boy with multiple tumors identified at initial presentation, with histology consistent with soft tissue ganglioneuromas and an abdominal intermixed ganglioneuroblastoma. Although metastatic disease was present upon presentation, based on the histological subtypes of his tumors, the likelihood of progressive disease was low. Therefore, he was observed without active treatment and remains well without disease progression almost 1-year following diagnosis. As both ganglioneuromas and intermixed ganglioneuroblastomas have only case reports of metastatic behaviour in the literature, this case provides further support for the maturation of what was likely once a more immature and malignant tumor.

Keywords: Ganglioneuroma; Metastatic; Ganglioneuroblastoma; Pediatric

Introduction

Neuroblastic tumors account for 8-10% of all pediatric solid tumors and 80% of those found in patients under 5 years of age [2]. They are tumors of the sympathetic nervous system that arise in the adrenal medulla, sympathetic ganglia and paraganglia [3], and occur most commonly in adrenal glands (35%), paraspinal retroperitoneal ganglia (30-35%), posterior mediastinum (20%), head and neck (1-5%) and pelvis (2-3%) [4]. Approximately 1% of neuroblastic tumors metastasize, generally via the vascular or lymphatic system, most commonly to the liver, lung, bone or bone marrow [5].

Neuroblastic tumors have an age-linked classification that is dependent on the differentiation of the neuroblast and the presence or absence of Schwannian stromal development [1]. On this basis, neuroblastic tumors are classified into following 4 categories: 1) Neuroblastoma, 2) Ganglioneuroblastoma intermixed, 3) Ganglioneuroblastoma nodular, and 4) Ganglioneuroma [1]. The most immature type of these tumors is a neuroblastoma, with a ganglioneuroma representing the final stage of maturation among the neuroblastic tumors. It is thought that all ganglioneuromas were once a neuroblastoma at an earlier time in their development [1].

Immature tumors tend to be aggressive and occur in younger children (median age 2), where more mature tumors tend to occur in older children (median age 7 years) and behave in a more benign fashion [2].

Ganglioneuromas tend to be isolated masses in sites compatible with a primary neuroblastoma without distant metastases [6]. Three large studies assessing neuroblastic tumors in pediatric patient populations demonstrated benign behaviour with no evidence of tumor-related mortality in patients with ganglioneuromas or intermixed ganglioneuroblastomas [7-9]. In a study assessing 2286 neuroblastic tumors, all ganglioneuromas were localized, occurring in the thorax, abdomen, pelvis or neck [7]. Similarly, in a study of 746 neuroblastic tumors, ganglioneuromas and intermixed ganglioneuroblastomas had only localized disease [9]. In a study with 552 cases of neuroblastic tumors, all patients in the ganglioneuroma subtype had unifocal disease with no evidence of distant metastases. There were 2 patients with metastatic disease in the intermixed ganglioneuroblastomas, one with a lymph node and the other adenoid involvement [8].

We report an unusual presentation of multiple metastatic ganglioneuromas in a young patient with whom we simultaneously identified an intermixed ganglioneuroblastoma. There are many factors that make this case unique. To our knowledge, it is the first to identify simultaneous stages of tumor maturation in different tumor sites upon initial presentation in a pediatric patient. The finding of multiple ganglioneuroma in somatic soft tissue and at such a young age is also very uncommon in the literature.

Case Presentation

A previously healthy 3-year-old boy, with no symptoms consistent with Carney's complex or Costello syndrome, presented with a mass on the posterior aspect of his right thigh that was increasing in size over a 1-month period. He was otherwise well with no constitutional symptoms, rashes, abdominal pain or diarrhea. An MRI of his thigh revealed 3 well-circumscribed lesions within the right biceps femoris muscle (2.6 x 2.4 x 4.9 cm), vastus lateralis muscle (1.3 x 0.8 x 2.3 cm) and vastus medialis muscle (0.8 x 0.5 x 2.1cm). A biopsy of these lesions showed organoid bundles and fascicles of Schwann cells (S-100 protein positive) surrounded by a layer of perineurial cells positive for EMA and GLUT-1. Scattered throughout were large ganglion cells with copious amphophilic cytoplasm and large nuclei with prominent nucleoli that stained positive for synaptophysin but were negative for desmin. N-MYC amplification was not present. This was in keeping with a ganglioneuroma.

This rare presentation of a multifocal ganglioneuroma in somatic soft tissue raised the possibility

that these lesions could represent fully matured metastases from a primary, less mature lesion. Therefore, a metastatic work-up was performed, which included an abdominal MRI and CT scan of the thorax. They revealed masses in the right adrenal fossa (2.6 x 1.9 x 3.7 cm) and a soft tissue mass abutting the left hemidiaphragm (3.3 x 1.8 x 3.3 cm) with expansion of the left 8th rib, likely representing infiltration. The remainder of the staging work-up, including a bone scan, bilateral bone marrow aspirates and biopsies, and a MIBG scan were unremarkable. Urine vanillylmandelic acid (VMA) and homovanillic acid (HVA) to creatinine ratios were within normal limits at 5 mmol/mol UCR and 13 mmol/mol UCR, respectively. The patient underwent a complete resection of the adrenal mass. This pathology was in keeping with a favorable histology intermixed ganglioneuroblastoma that was Schwannian stroma rich, with no evidence of N-MYC amplification or ALK gene mutation.

Given that the adrenal lesion was completely resected and that intermixed ganglioneuroblastoma and ganglioneuromas have a low malignant potential, we felt that the risk of disease progression was low. The potential harm from treatment was felt to be higher than the risk of disease progression, and there was likely no benefit of chemotherapy to a matured tumor, therefore no chemotherapy was provided and the decision was to monitor for disease progression with serial imaging. Follow-up scans seven months after the initial presentation show stable disease. And, almost 1-year after presentation, there is no clinical evidence of disease progression.

Discussion

There are very few pediatric cases of metastatic intermixed ganglioneuroblastoma and to our knowledge this is only the second pediatric case where an intermixed ganglioneuroblastoma has metastasized to give rise to multiple soft tissue ganglioneuromas [13]. In the previous case, the patient had somatic soft tissue masses and an adrenal mass in the first few months of life that were not initially biopsied. The diagnosis of ganglioneuroblastoma was not made until 2 years after the initial presentation and presumably represented a neuroblastoma that had matured with time. The further maturation of these soft tissue lesions to ganglioneuromas occurred over a 6 year period after the initial presentation and was not diagnosed concurrently as with our case. To our knowledge, this is the first pediatric case with concurrent adrenal ganglioneuroblastoma and multiple soft tissue ganglioneuroma metastases at the initial presentation.

There are limited case reports of metastatic intermixed adrenal ganglioneuroblastoma in the literature [5,14, 15]. However, with these cases, the metastatic tumors were identified from 1 year to 3 years after the initial presentation and not concurrently as with the case we

present. There is only one other case in the literature where the primary (adrenal) and metastatic (orbit) tumor sites were both identified at the initial presentation.

In this case, unlike our patient, there was similar histology in both the primary and metastatic sites and did not show evidence of tumor maturation in the metastases as with our patient. Furthermore, they had elevated urine catecholamine levels, and N-MYC amplification and ALK gene mutations were not tested, which raises the possibility of a more unfavorable histology in this particular patient, which would account for its metastatic potential [16]. Our patient had favorable histology, which makes the metastases of his tumor more unlikely.

Neuroblastomas have the capability of maturing spontaneously to ganglioneuroblastomas and ganglioneuromas [6, 10-12]. Given that it is very uncommon for both ganglioneuromas and intermixed ganglioneuromas to metastasize, it is possible that our patient may have initially had a malignant neuroblastoma that metastasized and that both this initial tumor and the metastatic lesions

underwent spontaneous maturation. Our case further demonstrates that neuroblastic tumors have the capability to mature spontaneously and may not require chemotherapy to ensure an event-free survival. Although we are as of yet not able to definitely determine which neuroblastoma tumors will mature without treatment, given the long-term side effects associated with chemotherapy, it seems appropriate to monitor mature lesions such as ganglioneuromas and intermixed ganglioneuroblastomas, even those that are metastatic, given their low risk for ongoing progression.

Learning Points:

- 1) Ganglioneuromas and intermixed ganglioneuroblastomas have a low malignant potential with very good overall survival without treatment.
- 2) An observational approach to treatment appears to be appropriate in patients with mature neuroblastic tumors.
- 3) Neuroblastic tumors have the ability to mature without treatment as evidenced by the varying stages of tumor maturation seen in our patient.

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