


BRIEF REPORT

PD-1 inhibition in congenital pigment synthesizing metastatic melanoma

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Abstract

A newborn female child was born with a congenital pigment synthesizing melanoma of the scalp. Further workup revealed metastatic disease within the liver, lungs, and left tibia. Whole exome sequencing was performed on multiple samples that revealed one somatic mutation, lysine methyltransferase 2C (KMT2C), at low allelic frequency but no v-Raf murine sarcoma viral oncogene homolog B (BRAF), NF-1 mutation. Programmed death ligand 1 was moderately expressed. Treatment was initiated with the programmed cell death protein 1 inhibitor nivolumab. The patient tolerated this treatment well with minimal toxicity. She is now over a year out from initial diagnosis, continuing on nivolumab, with stable disease.

KEYWORDS

congenital, metastatic melanoma, PD-1 inhibition, pediatric, pigment synthesizing

1 | CASE

A newborn female child was noted to have a dark raised scalp lesion (Fig. 1). The lesion expanded and became more raised. The patient underwent excisional biopsy. Initial pathology was consistent with malignant blue nevus. A second review revealed pigment synthesizing melanoma (Fig. 2A), 7.3 mm in depth with 2 mitoses/mm². There were positive margins but no ulceration or angiolymphatic invasion. Some areas were consistent with preexisting sclerotic blue nevus and there were overlapping features with malignant blue nevus. A chest radiograph was negative and abdominal ultrasound demonstrated two suspicious lesions. Magnetic resonance imaging (MRI) revealed six hepatic lesions. She underwent biopsy of these and pathology was consistent with metastatic melanoma (Fig. 2B). Brain MRI and bone marrow examination were negative. Whole body positron emission tomography (PET) imaging revealed disease in her left posterior cervical chain (standardized uptake value [SUV] 2.9), lung (SUV 2), liver (SUV 3.1), abdomen (SUV 9.24), and left tibia (SUV 10.4) with a pathologic fracture. Microarray analysis from the liver lesion identified a gain of chromosome 6 and chromosome 9. The patient's mother had remained healthy throughout the pregnancy without any melanoma history or concerning skin lesions on full dermatologic examination.

The patient was enrolled on a prospective integrative clinical sequencing trial (PEDS-MIONCOSEQ) and underwent paired



FIGURE 1 Initial appearance of the scalp lesion prior to resection

tumor/normal whole exome sequencing and tumor transcriptome sequencing (RNA-Seq). Specifics of the sequencing procedure and bioinformatics analysis have been described previously.¹ Only one somatic mutation, lysine methyltransferase 2C (KMT2C) (mixed lineage leukemia protein 3 [MLL3], p. N729D), was detected at a low allelic frequency (7%) in a second sample while on treatment for 16 weeks. This somatic mutation was not seen in the original biopsy. No mutations were detected in v-Raf murine sarcoma viral oncogene homolog B (BRAF), NRAS, and TSC1/2 genes and no pathogenic variants were detected on germline sequencing. No remarkable gene copy number changes or driving fusions were detected. Programmed death ligand 1 (PD-L1) was moderately expressed.

Abbreviations: MLL3, mixed lineage leukemia protein 3; MRI, magnetic resonance imaging; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PET, positron emission tomography

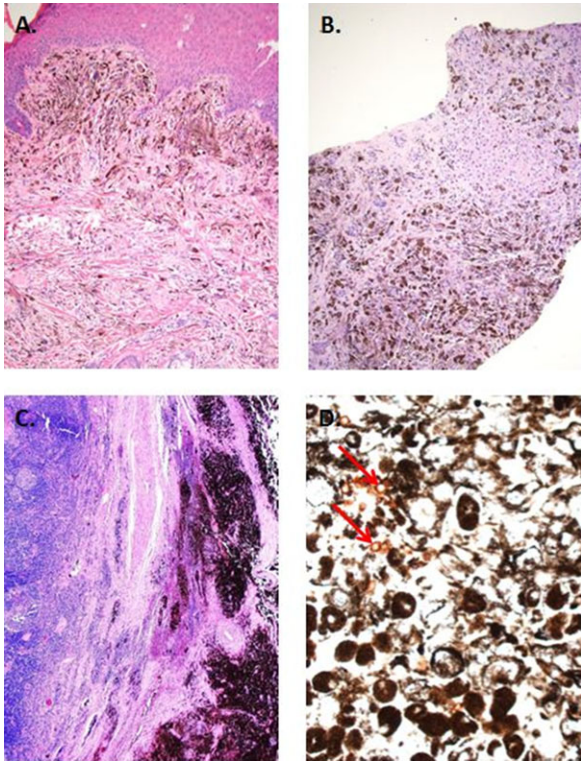


FIGURE 2 Skin biopsy with atypical spindled and epithelioid heavily pigmented melanocytic cells in the dermis (A). Similar atypical melanocytic cells noted in the liver (B) and lymph node (C). Few CD8 positive small lymphocytes (arrows) are noted adjacent to the melanoma cells (D)

Treatment was initiated with nivolumab, a programmed cell death protein 1 (PD-1) inhibitor, dosed at 3 mg/kg every 2 weeks. First dose was 50%, second dose 75%, and subsequent dosing at 100%. With the first dose, she developed Grade II diarrhea² that resolved quickly and did not recur. Following her first treatment, she developed a raised bony scalp lesion, concerning for progressive disease versus pseudo-progression. Following her third treatment, she developed left sided posterior cervical lymphadenopathy. With subsequent treatments, parents noted that the bony lesion and lymphadenopathy increased in size following treatments, and regressed prior to her next treatment. Reassessment of disease status was performed after six doses with whole body PET scan and abdominal MRI. The PET scan demonstrated significant lymphadenopathy, which clinically had not been present at initial PET scan, an increase in her pulmonary nodule, and otherwise stable disease. Abdominal MRI showed a slight increase in hepatic lesion size. A lymph node biopsy was performed following her eighth dose. Pathology revealed metastatic melanoma with large areas of coagulative necrosis (Fig. 2C). This could be consistent with treatment effect but necrosis has also been described within untreated lesions, although was not seen in initial pretreatment biopsies in our patient.³ 1–2% of tumor cells were weakly positive with PD-L1 by immunohistochemistry and a small number of CD8 positive infiltrating lymphocytes were noted nearby (Fig. 2D). Given evidence of treatment effect, clinical stability, and tolerance of therapy, the decision was made to continue with nivolumab. Disease evaluation was performed

following 14 doses with whole body PET and abdominal MRI. PET scan demonstrated stable number and size of lesions, with global decreased avidity (SUV maximum of 3.8). MRI of her abdomen showed stable number of lesions with a slight decrease in size. Following her 16th dose, she developed Grade I anemia (hemoglobin 10.2 g/dl) and Grade III neutropenia (absolute neutrophil count nadir 0.8 K/ μ l).² Repeat disease evaluation following 35 doses revealed stable disease.

2 | DISCUSSION

Childhood melanoma has been reported to account for 0.3–0.4% of all melanoma⁴ and between 1 and 3% of pediatric malignancies. Congenital metastatic melanoma is an extremely rare condition that is defined as metastatic melanoma recognized at birth. Its incidence is difficult to determine given its rarity. Congenital melanoma is generally subdivided into three separate entities based on etiology: (1) transmission from an affected mother by metastatic spread through the placenta, (2) primary de novo cutaneous congenital melanoma arising in utero, and (3) primary melanoma arising within a giant congenital melanocytic nevus.⁵

Pigment synthesizing melanoma, an uncommon variant, typically present as blue-black papules and its incidence is skewed toward the first or second decade of life.⁶ The most common location is the scalp. It is generally known as a low-grade malignancy.⁷ It has the tendency to recur locally with satellite nodules and regional lymph node spread but distant metastasis is rare. In a review of 190 cases of pigment synthesizing melanoma, only seven (3.7%) were congenital and only two (1.1%) presented with distant metastases. One congenital case was found to have lymph node and liver disease multiple months after presentation.⁸ Due to this rarity, optimal treatment is unknown. Additionally, treatment of metastatic melanoma has historically been unsuccessful. Biological basis of neonatal melanoma is unknown. They are usually not driven by BRAF. Our tumor had a low-frequency MLL3 mutation that has been reported in other relapsed/refractory solid tumors and lymphoma.^{9,10} No pathogenic variants were reported in germline sequencing that was reassuring and consistent with otherwise negative family history of cancers.

Nivolumab, a fully human immunoglobulin G4 human antibody to the PD-1 immune checkpoint, has been approved for the treatment of patients with metastatic or unresectable melanoma since 2014. By blocking PD-1, nivolumab restores anticancer immune responses through abrogation of T-cell inhibition mediated through the PD-1 pathway. A large phase III study in previously untreated adults with metastatic melanoma with wild-type BRAF demonstrated overall 1 year survival of 72.9%, median progression free survival of 5.1 months, and an objective response rate of 40%,¹¹ significant improvements over prior standard of care. Common adverse events seen included nausea (16.5%), fatigue (19.9%), and pruritus (17.0%). Additionally, checkpoint inhibitors have been associated with autoimmune toxicities ranging from colitis to endocrinopathies. In general, the PD-1 inhibitors seem to have less severe toxicities, with fewer severe adverse effects and decreased rates of discontinuation due to toxicity. This has been postulated to be due to the fact that CTLA-4 inhibitors

activate a wider range of T-cell subtypes.¹² Furthermore, autoimmunity secondary to PD-1 inhibition tends to occur later in the treatment course (at a median of 59–64 days) and is more likely to involve thyroid dysfunction rather than colitis or hypophysitis.^{13,14} We have conducted regular screening assessments for endocrine dysfunction, as well as clinical monitoring, and plan to continue this throughout her treatment course.

Only one published study exists looking at checkpoint inhibition in pediatric populations.¹⁵ Toxicities of this treatment were similar to that seen in adults but unfortunately no objective responses were observed. There are no published data on checkpoint inhibition in infancy. The efficacy of this approach in infants with immature immune systems is unknown. However, data showing cord blood with increased expression of the PD-1 molecules on CD4+ T cells in comparison to adult peripheral blood upon activation raise the possibility of utility in this population.

This case demonstrates the safe use of PD-1 checkpoint inhibition in a young infant.¹⁶ Our patient initially experienced some early Grade I–II diarrhea and later developed Grade II anemia and Grade III neutropenia, none of which required a change in therapy. She has continued to grow and develop normally. Following initiation of nivolumab, she developed left-sided posterior cervical lymphadenopathy. Given later improvement, this likely represents pseudo-progression, a phenomenon that is seen with the new immunotherapies during which an initial increase in tumor size is seen prior to subsequent improvement. On follow-up radiologic and clinical evaluations, our patient continues to demonstrate stable disease. Pigment synthesizing melanoma tends to be an indolent disease so it is difficult to ascertain exactly what contribution the nivolumab has made to her clinical stability. However, given lack of significant toxicity, overall tolerability, and stable disease, we plan to continue this treatment. If she develops progressive disease, consideration will be given to combination therapy with CTLA-4 inhibition.

ETHICS STATEMENT

Informed consent from the patient's mother was obtained and properly documented for publication of photographic image.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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