Congenital tumor

Claudia Maria Salgado, MD. PhD.
Children’s Hospital of Pittsburgh, Pittsburgh USA
31st European Congress of Pathology - 2019, Nice, France
Congenital (≤2 weeks) / “tumor” 2000 to 2018 at Children’s Hospital of Pittsburgh

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>LOCATION</th>
<th>NUMBER OF CASES</th>
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<tbody>
<tr>
<td>Teratoma</td>
<td>Sacroccideal</td>
<td>19</td>
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<tr>
<td></td>
<td>Neck</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Brain</td>
<td>1</td>
</tr>
<tr>
<td>Fetus in Fetus</td>
<td>Sacroccideal</td>
<td>1</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Retroperitoneal and others</td>
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<tr>
<td>Pleuropulmonary blastoma</td>
<td>Lung</td>
<td>1</td>
</tr>
<tr>
<td>Poorly diff epithelial TU</td>
<td>Liver</td>
<td>1</td>
</tr>
<tr>
<td>Malignant melanocytoma</td>
<td>Genital</td>
<td>2</td>
</tr>
<tr>
<td>Congenital fibrosarcoma</td>
<td>Extremities</td>
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<tr>
<td>Rhabdomyoma</td>
<td>Heart</td>
<td>1</td>
</tr>
<tr>
<td>Fibroma</td>
<td>Heart</td>
<td>1</td>
</tr>
<tr>
<td>Hemangioendothelioma</td>
<td>Liver</td>
<td>2</td>
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<tr>
<td>Granular cell tumor</td>
<td>Oral cavity</td>
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Clinical history

• The patient was born at term with no pre-natal or peri-natal complications.

• The physical exam showed approximately 15 small to medium size melanocytic nevi, ranging from 1.0 to 4.5 cm in largest diameter on his back and left leg.
Clinical history

- He was discharged to home and returned after 2 weeks because his mother noted enlargement of the head circumference, bulging fontanelle, generalized jerking movements and nystagmus.
- Brain CT - hydrocephalus, with enlargement of the 3rd and 4th ventricles and aqueduct stenosis.
- A VP shunt was placed.
Clinical history

• After the VP shunt, a full brain and spinal cord MRI revealed “diffuse nodular and confluent leptomeningeal enhancement throughout the brain stem, cerebellum and the entire spinal cord to include the cauda equina”.

• The patient was sent for consultation and follow-up with a dermatologist and a geneticist.

• The neurological symptoms improved, with only occasional seizures.

• His development and growth were normal for his age.
Clinical history

• At 18 months of age, the follow-up image studies showed a significant growth of the lower lumbar spine / cauda equina lesion, without other lesions in the brain or spinal cord.

• A laminectomy with biopsy of the cauda equina lesion was performed.

• Gross description: small multiple fragments of pink-tan soft tissue.
Diagnosis

• **MALIGNANT MELANOCYTIC PROLIFERATION IN THE SETTING OF NEUROCUTANEOUS MELANOCYTOSIS (SPINAL CORD PRIMARY “MELANOMA”).**

• **Target DNA sequence:** *NRAS Q61K* mutation.

• **Karyotype:** male karyotype with an unbalanced translocation between the short arms of chromosomes 1 and 4, that results in gain of 1p22 to 1pter; an unbalanced translocation between the long arms of chromosomes 13 and 14 that results in gain of the distal 13q and loss of distal 14q; gain of chromosomes 8 and 20, a ring chromosome 10 with loss of the majority of 10p and 10q and a ring chromosome 18.

• **Microarray:** multiple segmental chromosomal copy number alteration, including gain of 1p36.33p22.1 and loss within 4p16.3, gain of whole chromosomes 9 and 20 and gain of 13q14.2q34 and loss of 14q24.1q32-33, consistent with the chromosome analysis finding of an unbalanced der{14}t{13;14}.
Follow-up

• After his initial laminectomy and biopsy, the patient evolved with loss of ambulatory ability, gaze abnormalities and imaging signs of progressive disease in the spinal cord and central nervous system.

• He was treated with MEK inhibitor therapy (trametinib) but the process continued until death, proceeded by significant ascites, in hospice care.

• A full autopsy was performed at the UPMC Children’s Hospital of Pittsburgh.
Autopsy
In a prospective study, Walton et al (1976)

- 3.9% of the newborns had pigmented lesions.
- 1.01% - melanocytic nevi by Biopsy

- CMN > 40 cm called large/giant congenital nevi (L/GCMN) - 1 per 500,000 newborns.
- One of the most serious complications of CMN is Neurocutaneous melanocytosis (NCM).
Discussion - Neurocutaneous melanocytosis

• NCM is characterized by the presence of neoplastic pigment cells in the leptomeninges and/ or CNS, in association with large or multiple CMN.

• CMN features that carry an increased risk of NCM include, **large size, multiple satellite lesions**, and location at the posterior axis.

• However, in some patients, a low number of small nevi, like those seen in our patient, may also be associated with aggressive NCM and lead to a lethal outcome.

44 patients were evaluated with MRI and 16 were diagnosed with NCM.

- **NRAS Q61** mutations (K or R) were detected in 12 (75.5%).
- **BRAF V600E** mutation in 2 (12.5%).
- Two patients were negative for both mutations.
Classifying Melanocytic Tumors Based on DNA Copy Number Changes

Discussion

Malignant transformation in NMC are also associated with chromosomal abnormalities and additional mutations.

Amplification of mutated NRAS leading to congenital melanoma in neurocutaneous melanocytosis

Cláudia M. Salgado, Dipanjan Basu, Marina Nikiforova, Ronald L. Hamilton, Robin Gehris, Regina Jakacki, Ashok Panigrahy, Svetlana Yatsenko and Miguel Reyes-Múgica

Copy number abnormalities in new or progressive ‘neurocutaneous melanosis’ confirm it to be primary CNS melanoma

Veronica A. Kinsler1,2,6 · Satyamanasa Polubothu1,2,6 · J. Eduardo Calonje3,7 · W. Kling Chong4,8 · Dominic Thompson5,8 · Thomas S. Jacques6,8 · Deborah Morrogh5,8
Discussion - Treatment

• **Surgical intervention** in the context of symptomatic NMC with or without malignant transformation is important in confirming the diagnosis and relieving the symptoms. However, it is not curative.

• Multiple treatments have been reported in the literature, including radiation, immunotherapy, and target therapy for specific genetic alterations.

• Unfortunately, none of the described therapeutic interventions has been found to control the progression of the disease.

• In the current patient, despite targeted MEK inhibitor therapy, the disease progressed.
The Dual PI3K/mToR Inhibitor Omipalisib/GSK2126458 Inhibits Clonogenic Growth in Oncogenically-transformed Cells from Neurocutaneous Melanocytosis

DIPANJAN BASU\textsuperscript{1}, CLÁUDIA M. SALGADO\textsuperscript{1}, BRUCE BAUER\textsuperscript{2}, YASMIN KHAKOO\textsuperscript{3,4}, JANKI R. PATEL\textsuperscript{5}, RYAN M. HOEHL\textsuperscript{5}, DOMINIQUE M. BERTOLINI\textsuperscript{5}, JOIE ZABEC\textsuperscript{5}, MORGAN R. BRZOZOWSKI\textsuperscript{5} and MIGUEL REYES-MÚGICA\textsuperscript{1}
Discussion – peritoneal seeding

• One of the most ominous signs of disease progression in our patient was the peritoneal tumor “seeding”.
• This phenomenon has been recorded a few times in the literature.
• However, we have seen other cases in which V-P shunting did not cause peritoneal seeding, which raises the question of what mechanisms mediate this phenomenon.
Malignant Transformation in Neurocutaneous Melanosis

Andrew R. Guajardo MD, Christopher J VandenBussche MD, PhD, D Ashley Hill MD, PhD
Miguel Reyes-Múgica MD, Cheng-Ying Ho MD, PhD

Department of Neuropathology, The Johns Hopkins Hospital/Department of Pathology, Children’s National Medical Center
Department of Pathology, Children’s Hospital of Pittsburgh

ABSTRACT

**Background**

Neurocutaneous melanosis (NCM) is a rare congenital disorder characterized by somatic nevi and subependymal glioma. While the majority of the nevi are cutaneous, symptomatic complications and malformations can dramatically worsen prognosis. The exact mechanism and full extent of genetic determination are not entirely understood. However, early developmental somatic mutations are implicated in the pathogenesis of NCM.

**Design**

We performed a complete autopsy of a 9-year-old female with NCM status post a ventriculoperitoneal (VP) shunt. She presented with multiple subependymal gliomas and multiple cutaneous nevi. Whole genome sequencing revealed a somatic BRAFV600E in the glioma and a somatic NRASQ61R in the cutaneous nevi. Additionally, Copy Number Variation (CNV) analysis and targeted panel sequencing were used on the tissues.

**Results**

Malignant transformation of the glioma was confirmed by immunohistochemistry and BRAFV600E enrichment in malignant glioma. While sequencing showed a mutation in NRAS Q61R in both glioma and malignant melanocytic nevi, BRAFV600E was present in a subset of subependymal ganglion cell astrocytomas, including 9q34.3 (DRG/BrE408 derivatives; Gm2023; wild type), 11q23.1-23.2 (schizophrenic), 11q21.1, and 11q12.3-13.1, and one subset had the predicted redox sensitive G514R, adding to the malignant melanoma in NCM. The malignant brain nevus demonstrated a p53 mutation and DDX10 amplification, while BRAF amplification showed alterations in chromosome 9q34.3, 14q11.2, and 11q23.1. These findings are consistent with the hypothesis that somatic mutations in BRAFV600E are associated with malignant melanosis.

**Conclusions**

The novel application of targeted sequencing and CNV analysis allowed identification of a new molecular mechanism in NCM. This study highlights the importance of comprehensive genetic analysis in NCM and suggests that targeted therapy may be a viable option for the treatment of malignant melanosis.

**Figure 1**

A) Coronal section demonstrating pigmented lesions of bilateral hippocampi. B) Turbid abdomen due to peritoneal tumor; multiple satellite nodules are evident. C) H&E of brain cerebellar lesion. D) H&E of mononuclear neovascularity in the posterior fossa.

**Figure 2**

Gross photograph demonstrating multiple nodules along the small intestine.

**Figure 3**

H&E of malignant melanoma involving the abdominal viscera.

**REFERENCES**


**Table**

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<thead>
<tr>
<th>BRAF Mutations</th>
<th>NRAS Mutations</th>
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<tbody>
<tr>
<td>V600E</td>
<td>Q61R</td>
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<thead>
<tr>
<th>Conclusion</th>
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<tr>
<td>An NCM, but not a BRAF mutation was found in all melanocytic lesions, however, blood, lymph node, and other neurocutaneous tissues were negative for confounding genomic mutations.</td>
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<td>Due to actively pigmented lesions demonstrating the same NRAS mutation, a single stepwise progression of a nevus to melanoma is possible.</td>
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<td>Confirmation of the malignant subtype may allow targeted options such as susceptibility to MEK inhibitors.</td>
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<td>It is possible that malignant melanocytes were shed into the abdomen via the VP shunt, but no malignancy was discovered in the CNS or the peritoneum.</td>
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Using novel methods, this study demonstrates the potential for malignant transformation in the nevus of NCM patients and highlights the need for improved management strategies in this disease.
Take home messages

• Although NCM is usually seen in patients with extensive skin involvement by congenital nevi, patients born with few and relatively small CMN may also suffer this condition.
• The need to relieve hydrocephalus by V-P shunting carries a significant risk of peritoneal seeding in patients with NCM, whose mechanisms are still unexplored.
• Monitoring of this complication is strongly advised.
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17 to 19th October 2019
Pittsburgh - USA