# INTRACRANIAL NEUROBLASTOMA METASTASIS WITHOUT MYCN AMPLIFICATION

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## Case Report

In March 2019, a one year and eight months old boy was admitted to the hospital with a history of a growing painless nodule on the left parieto-occipital region, abdominal distension, hepatomegaly, weight loss and irritability. The infant was first submitted to an abdominal ultrasound that shown multiple hepatic nodules associated with abdominal lymphadenopathy. Magnetic Resonance Imaging (MRI) of the head showed an extra-axial, well delimited, contrast enhancing, homogeneous lesion on the fronto-parietal region, measuring 54x53x43mm, compressing the underling brain and causing a contralateral shift of midline, as well as infiltrating the dura mater and invading the adjacent frontal and parietal bones(*). A neck Computerized Tomography (CT) scan showed mild lymphadenopathy, while abdominal MRI showed multiple heterogeneous contrast enhancing lesion on the liver, and a left sided retroperitoneal mass measuring 46x34x32mm with heterogeneous contrast enhancement arising from the ipsilateral adrenal gland in association with disseminated abdominal lymphadenopathy. A CT scan of the thorax did not show any abnormality. Blood samples revealed elevated levels of vanillylmandelic acid, homovanillic acid lactate dehydrogenase.

Due to the midline shift with sings of cerebral herniation, the patient underwent neurosurgery on March 22nd, 2019, with gross total resection of the intracranial lesion and adjacent dura-mater and bone. Histopathology and immunohistochemistry showed a highly cellular, poorly differentiated malignant tumor consisting of small cells and invading the bone compatible with the diagnoses of poorly differentiated Neuroblastoma. Fluorescence in situ hybridization (FISH) revealed absence of NMYC amplification. Bone scintigraphy demonstrated areas of increased tracer activity on both parietal bones, spinous process of T9, and vertebral bodies of L1 to L5. Bilateral bone marrow biopsy revealed neoplastic infiltrative cells. According to the International Neuroblastoma Staging System and the Children´s Oncology Group risk stratification for children with neuroblastoma the patient was stratified as Stage 4, high risk respectively. The patient received five cycles of chemotherapy, each cycle consisting of four phases alternating combination of cyclophosphamide, topotecan, doxorubicin, carboplatin and etoposide. During the interval between the phases of each cycle the patient received filgrastim.

After receiving the fourth chemotherapy cycle the patient was reassessed for treatment response. Abdominal MRI revealed minimal residual hepatic lesions, over 30% decrease in size of the primary retroperitoneal lesion arising from the left adrenal gland and almost complete resolution of abdominal lymphadenopathy with only few enlarged retroperitoneal lymph nodes. Bone scintigraphy revealed complete resolution of the previous lesions and bone marrow biopsy showed no tumor infiltration. Despite the partial response to treatment, ten months past the initial diagnosis, the patient evolved with febrile neutropenia during the fifth cycle of chemotherapy and died from infectious complications before completing the protocol for autologous stem cell transplantation.

## Discussion

Neuroblastoma is the most common solid malignancy in children under 15 years of age, responding for up to 10% of all pediatric tumors and approximately 15% of all cancer related deaths.[1,2] It is an embryonal tumor deriving from neural crest cells that form the sympathetic nervous system.[1,2]

Neuroblastomas present a heterogeneous behavior ranging from spontaneous resolution to aggressive and treatment resistant presentations.[2,3] The most important factors related to the wide range of clinical presentations include patients age at diagnosis, disease extension, histopathological characteristics, and cytogenetic and molecular features such as ploidy, MYCN oncogene amplification as well as allelic losses in chromosomes 1p and 11q. [3,4]

Distant metastases are identified in 70% of the patients at the diagnosis and relate to poor prognosis.[4,5] The most common metastatic sites are liver, bone, and bone marrow.[6,7] Skull base, skull vault and the orbital bones may also be affected during primary or recurrent disease.[5,7] However, intracranial metastasis are a rare and serious complication of Neuroblastomas, relating to a significantly worse prognosis.[5,7,8] Neuroblastoma intracranial metastases are mostly seen in patients with advanced disease and MYCN amplification with some studies suggesting a one-year survival rate of less than 50%.[5,6,7]

Neuroblastoma treatment options depend upon tumor staging and risk stratification.[9,10] Treatment for aggressive tumors rely largely on induction chemotherapy, radiation therapy, autologous stem cell transplantation and surgical resection. [1,2,3,4,8,9] New treatment options include cellular differentiating agents, angiogenesis inhibitors, immunotherapy with antiganglioside antibodies, DNA alkylating drugs and radioactive 131I-MIBG. [1,2,3,4,8,14]

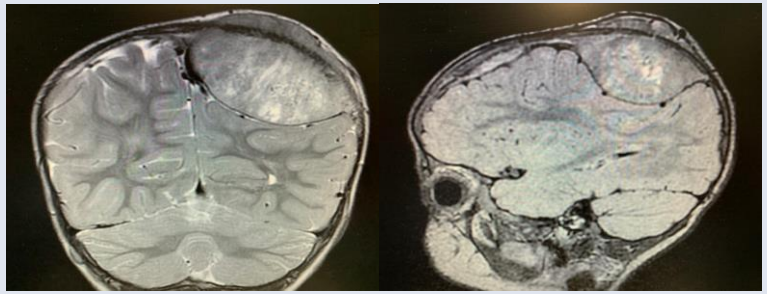

*Image 1: Head MRI

## Conclusion

Despite the advances in the comprehension of cytogenetic and molecular alterations involved in the pathogenesis of Neuroblastoma as well as the new treatment protocols based on risk stratification, the management of patients with this condition is still challenging, especially in patients with stage 3 and 4 diseases, in which the treatment itself imposes great risk of toxicity and comes associated with great morbidity and mortality. In addition, the concurrent presence of intracranial metastasis suggests an even more disheartening prognosis.

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