Congenital Neuroblastoma in a Neonate With Isotretinoin Embryopathy

Shiley Aguilar, MSN, RN, FNP-C,* Chrystal Louis, MD, MPH,* John Hicks, MD, DDS, PhD,† Peter Zage, MD, PhD,* and Heidi Russell, MD*

Summary: We describe a neonate with isotretinoin embryopathy and an incidental finding of congenital neuroblastoma. Diffuse liver metastases led to the decision to provide oncologic therapy followed by tumor resection. Despite the possible need for chronic care related to the comorbidities of the isotretinoin embryopathy and oncologic management, the patient remains disease-free. Because of the uncertain etiology of neuroblastoma, it remains unclear whether exposure to isotretinoin during embryogenesis and fetal development had an oncogenic effect on this patient.

Key Words: neuroblastoma, congenital, metastatic, isotretinoin embryopathy

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N euroblastoma (NBL) is derived from embryonal neural crest cells and is the most common solid neoplasm of childhood.1 Congenital NBL is diagnosed in the first 30 days of life and is the most common neonatal solid tumor malignancy, representing 30% to 50% of neonatal tumors. The use of ultrasound in the antenatal period has been instrumental in identifying incidental congenital NBL.2 These tumors tend to have a high rate of spontaneous tumor regression and a low risk of progression allowing observation of some localized tumors.3 However, when metastases are present at diagnosis, treatment is complex, as neonates can be sensitive to mechanical effects of tumors4,5 and to chemotherapy and radiation.6 Isotretinoin, a form of Vitamin A analogs known as retinoids, is a human teratogen and in utero exposure can cause multiple birth defects and malformations7 including craniofacial and cardiac birth anomalies. This constellation of cognitive dysfunction, and central nervous system, craniofacial and cardiac abnormalities is referred to as "isotretinoin embryopathy" (IE).8 Isotretinoin exposure between 2 and 5 weeks after conception seems to be the critical period; however, exposure during any time of pregnancy presents a high teratogenic risk.7,8 Isotretinoin also has anti-NBL effects and plays a role in treatment of high-risk NBL.9 To date, IE has not been associated with increased prevalence of neoplasms. Here, we present a case of IE associated with congenital metastatic NBL.

CASE

This child was born at 39 weeks’ gestation through forceps-assisted vaginal delivery with Apgars of 5 and 9 at 1 and 5 minutes, respectively. The mother reported using isotretinoin for up to 1 month after conception and was therefore followed in a high-risk obstetrics clinic. At birth, the neonate had normal weight and length but had an absent left ear, rudimentary right ear with missing auditory canal, choroid plexus cysts, a short nasal bridge, patent ductus arteriosus, and left-sided facial palsy.

Given the patient’s overall medical complexity, a thorough evaluation of the organ systems was performed, and a 3 × 3 × 2 cm right adrenal gland mass with multiple hypoechoic lesions was found on ultrasound and confirmed with computed tomography. The urine catecholamines (vanillyl mandelic acid, homovanillic acid) were elevated at 71.8 and 89.6 mg/g, respectively. No bone metastases were identified on technetium 99 bone scan.

At 2 weeks of age, a diagnostic right adrenalectomy, liver biopsy, and bone marrow aspirations and biopsies were performed. The surgeon performed a liver biopsy during the operative procedure as the organ appeared to be infiltrated with tumor upon visual inspection. Histopathologic examination of the right adrenal gland and liver biopsy provided the diagnosis of poorly differentiated NBL of the adrenal gland with an intermediate mitotic-karyorrhectic index (favorable histology) and metastatic NBL involving the liver with little minimal residual liver parenchyma (Fig. 1). The bone marrow and placenta were negative for metastatic tumor. FISH analysis showed 15q13.3 duplication, with no evidence of MYCN amplification. The 15q13.3 duplication, which has not been linked to NBL development, although it is known to be associated with developmental delay and seizures,10 was also found as a constitutional abnormality in the neonate’s father by high-resolution chromosomal microarray. A iodine-131-metaiodobenzylguanidine (MIBG) scan after adrenalectomy confirmed activity in the liver. The patient was determined to be stage IVS with favorable histology. On the basis of the patient’s age and extensive metastatic liver disease (Figs. 1B, C), a decision was made to treat the infant with intermediate-risk chemotherapy, including carboplatin, etoposide, cyclophosphamide, and doxorubicin with prophylactic granulocyte colony-stimulating factor.11

The patient’s chemotherapy course was complicated by a delay before course 2 due to congenital hypoventilation syndrome requiring ventilation support and G-tube placement and the development of a small bowel obstruction requiring surgical correction.

Although the liver lesions increased by <25% according to magnetic resonance imaging after cycle 2, scans obtained after the fourth cycle of chemotherapy showed complete resolution of disease. No additional chemotherapy was given. The patient is currently 2 years off therapy with no evidence of disease recurrence.

DISCUSSION

NBL is a tumor of heterogenous origin with clinical behavior ranging from spontaneous regression to aggressive metastatic disease.12 It is often diagnosed after discovery of a palpable abdominal mass or abdominal distension in an infant, although some tumors are identified in asymptomatic neonates during routine examinations.2,12 The NBL
in the present case was an incidental finding identified during an abdominal ultrasound to evaluate for systemic defects related to IE. IE is a causative factor in a variety of dysmorphisms and anomalies, affecting the central nervous system, heart, and craniofacial areas. This patient’s oncological finding was the distinguishing factor in this particular case. The marked systemic defects related to retinoid exposure coupled with the incidental finding of NBL are unique to both documented cases of IE and congenital NBL, alike.

Retinoids, such as isotretinoin, are Vitamin A analogs usually prescribed for the treatment of recalcitrant acne. The mechanism of action for their teratogenic effects is believed to be associated with cephalic neural crest cells, because of the distribution of the associated malformations. These compounds also have documented anticancer effects against NBL tumor cells in vitro and in vivo. Isotretinoin has been shown to reduce NBL cell proliferation, decrease MYC-N oncogene expression, and induce NBL cell differentiation. Phase I isotretinoin trials in children established a dose of 160 mg/m²/day, divided twice daily, and given for 2 consecutive weeks each month, as an effective antitumor dose with minimal and well-tolerated side effects. Treatment of high-risk NBL with isotretinoin after stem cell transplantation has increased event-free and overall survival. Retinoids function through interactions with retinoic acid receptors and activation of gene transcription. Retinoic acid-mediated pathways responsible for the antitumor effect in NBL are yet to be fully elucidated. Although recent studies have shown increased RET kinase expression in response to retinoic acid treatment, more recent studies have shown that the zinc-finger DNA protein ZNF423 is associated with the retinoic acid receptor complex and is required for retinoic acid-mediated gene transactivation and NBL differentiation, whereas loss of the tumor suppressor NF1 results in repression of ZNF423 and resistance to retinoic acid.

Stage IVS is a special stage of NBL. It has metastases to the skin, liver, or bone marrow in infants ≤ 1 year of age. Stage IVS NBL can undergo spontaneous regression and usually has an excellent prognosis with observation alone. Infants with extensive hepatic involvement, particularly those neonates that are symptomatic from mechanical complications, may be at a higher risk for death or long-term hepatic complications. We elected to give chemotherapy in this case because of the extensive liver...
involvement and because of a concern that isotretinoin exposure would modify the tumor’s behavior. Although the tumor grew after 2 cycles of chemotherapy, it eventually responded and complete resolution was achieved. Long-term follow-up and close collaboration with other medical specialties continues due to the complexities of the medical conditions in this child.

Because the NBL likely developed late in pregnancy and isotretinoin exposure occurred early, it is unlikely the drug provided any antitumor effect. In this child, there is no definitive method to determine whether exposure to isotretinoin early in embryogenesis had an oncogenic effect on neural crest development. There have been no reports of increased prevalence of neural crest-derived malignancies associated with IE. In contrast, the etiology of NBL remains unclear. This patient’s clinical presentation may provide insight into directions for future research toward understanding the relationship between NBL and isotretinoin.

REFERENCES