BRIEF REPORT
Neuroblastoma in Monozygotic Twins With Distinct Presentation
Pathology and Outcome: Is It Familial or in Utero Metastasis

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To date ten sets of monozygotic twins with neuroblastoma have been reported in the literature. Twin-to-twin in utero metastasis have been proposed as the mechanism of tumor development in the second twin; based on similar pathology, presence of metastatic disease, absence of a primary tumor, and/or later presentation in the second twin. Hereditary neuroblastoma has not been described in this context. We propose that primary neuroblastoma can occur in monozygotic twins without twin-twin transmission; due to the different ages of presentation, histology, ploidy, and tumor behavior. Pediatr Blood Cancer 2014;61:1124–1125. © 2013 Wiley Periodicals, Inc.

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INTRODUCTION

Neuroblastoma (NB) is the most common extracranial solid tumor in children. Classified as a neuroendocrine tumor, it arises from the neural crest elements anywhere along the sympathetic chain. Neuroblastoma is mainly a sporadic tumor but 1–2% of new patients have a family history of the disease [1,2]. Familial neuroblastoma is often diagnosed at an earlier age (usually infancy), has multiple primary tumors and shares the same diverse clinical behavior as sporadic neuroblastoma (ranging from aggressive progression to spontaneous regression) [3–6]. In monozygotic twins, neuroblastoma can either be concordant when both twins are affected or discordant when only one of the twins has the tumor. Ten pairs of monozygotic twins with neuroblastoma have been reported, most of whom shared histologic findings, leading to the postulation that concordance between twins is secondary to placental metastases [7,8]. We report monozygotic twins who developed neuroblastoma separately and propose primary familial origin rather than twin-to-twin transmission.

CASE REPORT

The patients were female monozygotic twins conceived by in vitro fertilization with donor sperm and born at 33 weeks’ gestation. Apart from prematurity no neonatal complications were noted.

Twin 1 presented at 5 months of age, with a large abdominal mass. Computed tomography (CT) scan showed left posterior paraspinal mass at the level of T7, bilateral adrenal masses and diffuses metastatic disease in the liver. Bone marrow was negative. A biopsy of the adrenal tumor showed neuroblastoma, with favorable Shimada histology, low mitosis-karyorrhexis index (MKI), ploidy of 1 and MYCN amplification. She was INSS stage of IV- high-risk NB and received chemotherapy as per COG-protocol A3973. This protocol consisted of six cycles of chemotherapy (cyclophosphamide, doxorubicin and vincristine for 4 cycles, and cisplatin and etoposide for two cycles), surgical resection (total adrenalectomy, partial hepatectomy, and cholecystectomy), then high-dose chemotherapy followed by autologous stem cell transplant (ASCT), and finally tumor bed radiation. Twin 1 was alive and well 3 years following completion of neuroblastoma therapy.

Twin 2 presented at 19 months of age with a mass behind her right ear. Brain CT-scan showed a large, right-sided posterior occipital mass with accompanying hydrocephalus. Biopsy of the mass was consistent with neuroblastoma that was poorly differentiated, unfavorable histology with MYCN amplification, ploidy of 1.93 and high MKI. Body CT showed large retroperitoneal mass encasing the celiac axis and portal vein, and a liver mass, without adrenal involvement. Bone scan and bone marrow evaluations were negative. She was started on the same chemotherapy regimen (COG-A3973). Following induction chemotherapy, scans showed almost complete resolution of neck mass, and marked improvement in her abdominal mass and liver lesions. She underwent total surgical resection of the tumor followed by myeloablative chemotherapy and ASCT. Six days post-ASCT; she developed breathing difficulties, abdominal distension and decreased urine output, veno-occlusive disease of the liver followed by progressively multisystem organ failure. Despite aggressive supportive care Twin 2 clinical status continued to deteriorate and eventually died 43 days post-ASCT.

DISCUSSION

Monozygotic twins who develop neuroblastoma can be concordant or discordant. Although most neuroblastomas occur sporadically, 1–2% are familial in origin [1,3–5], and are associated with multiple primary tumors, usually occurring in early infancy <18 months. Analysis of published pedigrees shows autosomal dominant inheritance and incomplete penetrance. The main question when considering the mechanism(s) of occurrence of congenital neuroblastoma in monozygotic twins is whether the diseases represent independent primary tumors as part of an

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inherited susceptibility to tumor development, or whether one twin receives metastatic tumor from the co-twin via placental anastomosis. Twin-to-twin in utero metastasis was the proposed hypothesis in most cases as evidenced by similar tumor pathology, the presence of metastatic disease in the second twin with absence of a primary tumor, and/or later presentation in the second twin [9]. Primary NB was described in two previous reports because of the presence of primary tumor site in both twins; however these reports were deficient regarding genetic and molecular characteristics of tumors [8,9]. In patients with hereditary or familial NB there is a remarkable heterogeneity. Within individual families, the disease can vary from asymptomatic and spontaneously regressing neuroblastoma to a rapidly progressive and fatal disease. Thus, the timing of inactivation of the second tumor suppressor gene allele and additional mutations are postulated to confer the ultimate clinical phenotype.

Fetoplacental or twin–twin metastases are favored when one twin manifests a readily identifiable primary tumor and the other twin manifests a metastatic disease, it is also considered when both tumors are identical and presents simultaneously or shortly thereafter. Independent primary tumors are favored when both twins display obvious primary tumors that are distinguishable clinically, histologically, molecularly, and by the age at presentation.

Upon review of the published literature, we found only 10 pairs of monozygotic twins who were concordant for neuroblastoma [7,8]. Almost all of these cases presented within the first 6 months of life, either simultaneously or <6 months apart. In six sets of twins, fetoplacental metastasis was considered, two sets were considered synchronous primary tumors and in the remaining two reports no conclusion could be made. In the two reports describing synchronous primary tumors information was deficient regarding genetic and molecular characteristics of tumors. Therefore confirming the mechanism of concordance of neuroblastoma would be difficult to fully conclude. We are reporting the eleventh set of NB concordance in monozygotic twins. We propose independent primary presentation of NB in both twins as a result of genetic predisposition. Our supportive evidence is the 14 months delay in initial presentation of the second twin, which makes fetoplacental metastases highly unlikely. Both presented with multiple primary sites and despite MYCN amplification in both tumors they exhibited different histopathology. PHOX2B gene was the first gene for which germline mutations were thought to predispose to familial neuroblastoma [10], most recently heritable mutations of ALK gene were found to be the main cause of familial neuroblastoma [2]. Even though we suggested familial neuroblastoma we could not prove it, because the twins were conceived by IVF using a donor sperm and the twins’ mother was adopted. ALK gene mutation analysis was not obtained on the surviving twin.

REFERENCES