Fanconi Anemia with Neuroblastoma Complicated by Acute Myelogenous Leukemia

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September 11, 2020

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Running Title : Fanconi Anemia and Cancer Predisposition

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Word count: 494 words

Number of Figures : 1

Key words : Fanconi anemia; acute myelogenous leukemia; neuroblastoma; cancer predisposition

To the Editor:

Fanconi anemia (FA) is an inherited disorder characterized by mutations that impair DNA interstrand crosslinks repair and result in genomic instability, sensitivity to cytotoxic agents, and cancer predisposition.[1] We present a case of FA with a VACTERL-like phenotype (anal, renal, cardiac, and limb defects) complicated by the development of two malignancies.

A one-day-old girl was referred for management of an imperforate anus and recto-vaginal fistula. She presented with microcephaly, microphthalmia, low set right ear, high-arched palate, choanal atresia, cutis aplasia, clinodactyly, and vertical talus. She had an atretic left kidney, ectopic right kidney, a patent foramen ovale, and a mid-muscular ventricular septal defect. A year later, surveillance abdominal ultrasonography detected a left upper quadrant mass. Computed tomography (CT) of the abdomen and pelvis defined a retroperitoneal mass and hepatic lesions with corresponding uptake on metaiodobenzylguanidine (MIBG) scan. Urine vanillylmandelic acid (VMA) was 209 ug/mg creat (normal <27), homovanillic acid (HVA) 116.1

ug/mg creat (normal <33), neuron-specific enolase (NSE) 87.8 ng/ml (normal <10.8). Pathology confirmed poorly differentiated MYCN non-amplified neuroblastoma of unfavorable histology, with DNA index 1, and loss of heterozygosity at 1p and 11q23. Following one cycle of chemotherapy per COG ANBL0531 with etoposide and carboplatin, the patient developed hypoxemic respiratory distress, mucositis, liver dysfunction, gastrointestinal bleeding, and persistent fevers. Prolonged pancytopenia prompted a bone marrow evaluation: dysplastic megakaryocytes were seen but did not meet criteria for myelodysplastic syndrome [**figure 1**] . In addition to a known 1p cytogenetic abnormality, 5q deletion, gain of chromosome 17, and additional material on 18q were detected. Subsequently, FA was diagnosed by Diepoxybutane (DEB) analysis on both blood and skin fibroblasts, and identification of a pathogenic mutation in PALB2. A month later, a bone marrow aspirate revealed acute myelogenous leukemia (AML) with 5q and 7q deletions. The patient passed away shortly thereafter from multiorgan dysfunction.

Less than 5% of infants with FA are diagnosed based on morphological features.[2] In a series of 419 patients, one-third lacked obvious congenital abnormalities.[3] Moreover, 18 of 54 (33%) patients with FA from the NIH Inherited Bone Marrow Failure Registry met criteria for VACTERL with hydrocephalus (VACTERL-H).

Furthermore, children harboring FANCD1/BRCA2 and FANCN/PALB2 mutations have an increased likelihood of developing a solid malignancy.[1] This child's PALB2 gene mutation encoding a BRCA2-interacting protein[5] may have contributed to the development of neuroblastoma. Children with these mutations have a cumulative incidence of leukemia of 80% by age 10 and chromosomal gains 1q, 3q, 13q, and monosomy 7 confer an increased risk.[6-8] We illustrate that patients with FA have a genetic cancer predisposition and their risk is likely also greater after exposure to chemotherapy.

Lastly, allogeneic hematopoietic stem cell transplantation was discussed. Strategies to reduce conditioning regimen toxicity and graft-versus-host disease related morbidity have been developed.[9-12] However, comfort care was favored given clinical deterioration.

This case highlights diagnostic and therapeutic challenges presented by this phenotypically heterogeneous disease and call for FA screening in patients suspect to have VACTERL to enable early diagnosis of the disease.

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