Burkitt Lymphoma and Williams Syndrome

A Model for Children With a Multisystem Disorder and Malignancy

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Summary: The authors describe a child with Williams syndrome who developed Burkitt lymphoma with a t(8;14). Williams syndrome is a contiguous gene syndrome that is not associated with a predilection for cancer. However, the management of a child with Williams syndrome and a malignancy is complicated by underlying disease in multiple organs. In 2001, the American Academy of Pediatrics published health care guidelines for children with Williams syndrome. These guidelines were adopted in the treatment of this child. Disease-specific guidelines should be applied to other children with multisystem disorders such as Down syndrome that require treatment of a malignancy.

Key Words: Williams syndrome, Burkitt lymphoma, American Academy of Pediatrics

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Williams syndrome (WS) is characterized by a distinctive facies including a flat nasal bridge and anteverted nares, a wide mouth with fleshy lips, periorbital fullness, epicanthal folds, a flat malar region, a small mandible, prominent ear lobes, and stellate iris.[1] Cardiovascular abnormalities, particularly supravalvular aortic stenosis, peripheral pulmonary artery stenosis, and hypertension, are characteristic. Psychomotor retardation and distinctive behavior are well described, and children have early language delay and later develop relative strengths in language and auditory memory.[1] Other characteristics include hoarse voice, hyperacusis, attention-deficit disorder, sleep difficulties, and anxiety. The children are very friendly and empathetic.[2]

WS is a contiguous gene syndrome caused by a 1.5-megabase microdeletion of chromosome 7, which is most often due to unbalanced recombination during meiosis.[3,4] Most patients with WS have a submicroscopic deletion of 7q11.23 detectable by fluorescence in situ hybridization (FISH).[5] The critical region encodes the elastin (*ELN*) gene, which contributes to supravalvular aortic stenosis, hoarse voice, and some of the characteristic facial features of WS. There are at least 25 other genes adjacent to the *ELN* gene that may also contribute to the phenotype.[4,6–8]

While there are reports of pancreatic adenocarcinoma, non-Hodgkin lymphoma, and mucinous cystadenoma of ovary in adult patients with WS and single cases of an astrocytoma and acute lymphoblastic leukemia in children with WS,[9–12] WS is not a cancer predisposition syndrome. In this report, we describe a case of Burkitt lymphoma (BL) in a child with WS and the application of the American Academy of Pediatrics (AAP) health care supervision guidelines in the management of this child.

CASE REPORT

Our patient was diagnosed with WS at 15 months of age during an evaluation for growth failure. Clinically, she had facial features consistent with WS (Fig. 1), supravalvular aortic and pulmonary stenosis, mild hypertension, and strabismus. The patient's constitutional karyotype from a mitogen-stimulated peripheral blood sample was 46,XX; however, a deletion of the *ELN* gene was observed in 100% of cells examined by FISH analysis. At 5 years of age she presented with an enlarging, firm, matted neck mass. Magnetic resonance imaging showed a mass centered in the left parapharyngeal space that encased and narrowed the internal carotid artery. The gallium-avid mass infiltrated the retropharyngeal space but did not extend intracranially or intraspinally. There were no associated metastases and the bone marrow and cerebrospinal fluid were not involved by the tumor. Epstein-Barr virus and toxoplasmosis serologies were negative.

The patient underwent fine-needle aspiration of a large left cervical lymph node followed by open biopsy of the node. Immunohistochemistry of the aspirate fluid and lymph node was consistent with BL. This was confirmed by flow cytometry that showed a monoclonal B-cell population with expression of dim CD10 and CD19, bright CD20, dim CD22, CD45, and FMC7, and moderate-intensity kappa light chain on the surface membrane. The karyotype obtained from the lymph node sample was 46,XX,t(8;14)(q24;q32)[cp2]/46,XX[3]. A duplication of the long arm of chromosome 1 [dup(1)(q32q22)], a common secondary chromosome abnormality in BL, was noted in addition to the t(8;14) in one metaphase cell. Interphase FISH analysis with a commercially available *MYC* probe showed rearrangement of the *MYC* gene in 20.4% (102/500) of the interphase cells examined (Fig. 2).

The patient received chemotherapy for approximately 4 months per Children's Cancer Group protocol 5961, regimen B1, for stage II BL. This protocol includes COP (cyclophosphamide 300 mg/m^2 IV, vincristine 1 mg/m^2 IV, and prednisone 60 mg/m^2 orally for 7 days), COPADM1 (cyclophosphamide 250 mg/m^2 IV every 12 hours for six doses, vincristine 2 mg/m^2 IV, prednisone 60 mg/m^2 orally for 5 days and then tapered, doxorubicin 60 mg/m^2 IV, and methotrexate

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FIGURE 1. Child with Williams syndrome.

3,000 mg/m^2 IV), COPADM2 (cyclophosphamide 500 mg/m^2 IV every 12 hours for six doses, vincristine 2 mg/m^2 IV, prednisone 60 mg/m^2 orally for 5 days and then tapered, doxorubicin 60 mg/m^2 IV, and methotrexate 3,000 mg/m^2), CYM1 and CYM2 (cytarabine 100 mg/m^2 IV every 24 hours for five doses and methotrexate 3,000 mg/m^2 IV), and COPADM3 (cyclophosphamide 500 mg/m^2 IV every 24 hours for two doses, vincristine 2 mg/m^2 IV, prednisone 60 mg/m^2 orally for 5 days and then tapered, doxorubicin 60 mg/m^2 IV, and methotrexate 3,000 mg/m^2 IV). Prophylactic intrathecal chemotherapy consists of methotrexate, cytarabine, and hydrocortisone. During the patient's care, we applied the AAP health care supervision guidelines for children 1 to 5 years with WS.[2] She completed the therapy without significant complications and has been in continuous remission for greater than 2 years.

DISCUSSION

This is the first reported case of BL in a child with WS. BL is a small, noncleaved B-cell lymphoma that accounts for 34% of cases of childhood non-Hodgkin lymphoma.[13] The incidence is 2 to 3 per million people in the United States.[13]

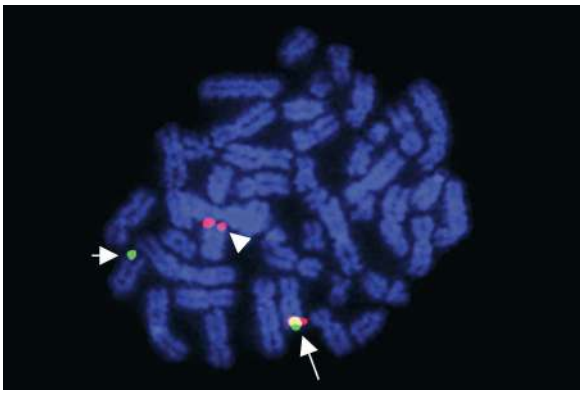

FIGURE 2. Metaphase cell from the patient's lymph node hybridized with a MYC break-apart probe (Vysis). The translocated chromosomes, der(8)t(8;14) (arrowhead) and der(14)t(8;14) (short arrow), are labeled by red and green signals, respectively. The normal chromosome 8 homolog (long arrow) has a yellow fusion signal.

WS occurs in 1 in 20,000 live births.[14] Although WS is a multisystem genetic disorder, it has not been associated with an increased risk of malignancy. To date, there is no known connection between the genetic consequences of the chromosomal abnormalities observed in WS and BL. The closest link is related to the *BCL7* gene family. The *BCL7A* gene was identified as being disrupted by a translocation through chromosome 12q24 in a BL cell line. BCL7B was identified within the WS deletion region and named for its homology to BCL7A. However, neither gene has been implicated in the etiology of both BL and WS.[15,16] At this time, one can only speculate whether the *BCL7* gene family provides a connection between WS and BL, and it appears that these two rare conditions occurred by chance in the same child.

To ensure the safe management of our patient, it was imperative to understand the natural history of WS and potential complications. The AAP recently published guidelines for the management of children with WS. These guidelines review the diagnosis of WS, describe the clinical features of WS by frequency and age, and offer anticipatory guidance from birth to 18 years of age.[2] For example, they provide many recommendations such as evaluation of growth, development, nutrition, and the cardiovascular system. We used the recommendations to avoid potential complications, refine our management, and improve the child's overall care.

The first issue encountered was during the preparation for a diagnostic surgical procedure requiring general anesthesia. We learned that there have been several reported cases of sudden death associated with anesthesia in patients with WS,[17] and one recommendation is to consult a pediatric anesthesiologist prior to any procedure with general anesthesia.[2] We followed this recommendation and made every attempt to limit the number of procedures, including those for disease surveillance.

As part of our patient's prechemotherapy evaluation, an echocardiogram was performed. This confirmed the patient's history of supravalvular aortic stenosis. The child's local cardiologist and our pediatric cardiology service followed the child throughout her cancer therapy. Repeat echocardiograms showed stable cardiac function. She continues to be followed annually by her cardiologist, as recommended by the AAP.

During the initial evaluation and induction chemotherapy, our patient had significant hypertension (>95% for age). WS patients are known to be at risk for essential hypertension as well as hypertension from aortic stenosis, renal artery stenosis, and infantile hypercalcemia, and these etiologies were considered during the patient's evaluation.[2] In this case, the etiology of the hypertension was most likely from both compression of the internal carotid artery by the lymphoma and the treatment of the lymphoma with glucocorticoids. The hypertension was treated with isradipine and clonidine. It resolved as the steroids were discontinued and the lymphoma diminished in size.

During the management of this patient, a WS-specific growth chart was used to follow her growth parameters. Children with WS often have growth failure and are smaller than age-matched controls. Our patient's height and weight were less than or equal to the 5th percentile on a standard growth chart but fell between the 10th and 50th percentile on a WS-specific growth chart. In addition to recommending

growth evaluations with WS-specific charts, the AAP guidelines recommend an assessment of feeding and nutrition at yearly visits, as 70% of children with WS have feeding difficulties. For example, these children may refuse food or eat only a small variety of foods. Since nutritional status is often compromised in children receiving chemotherapy, we took extra care to monitor the child's weight and nutritional status. This was especially important at times of mucositis, nausea, and vomiting. A clinical nutritionist met with the child and her family every 2 to 4 weeks and provided recommendations throughout treatment. We also learned from the guidelines that it is important for children with WS to avoid constipation, which may result in rectal prolapse.[2] Therefore, the nutritionist and clinicians provided suggestions to prevent constipation. In particular, provision of a stool-softening regimen was essential to prevent constipation that could lead to life-threatening sepsis, caused by medications such as vincristine that the child received as part of her chemotherapy regimen.

Another important preventive measure was referral to a pediatric dentist. The AAP guidelines recommend referral to a dentist during early childhood, because malocclusion and microdontia have a detrimental impact on oral hygiene.[2] The pediatric dentist evaluated our patient and taught the family how to provide mouth care. This was important to prevent increased caries formation during times of chemotherapy-induced mucosal breakdown and immune system compromise.

Lastly, throughout our patient's therapy it was necessary to understand the intellectual capacity, developmental stage, and any underlying anxieties of the child. The AAP recommends developmental evaluation and educational support with early intervention programs and school-based programs, and it provides information regarding the intellectual and developmental characteristics of children with WS.[2] Our patient was already receiving mainstream and special education classes as well as speech therapy. We provided a speech therapist during the child's hospitalizations, and child-life specialists provided developmentally appropriate games and activities.

Multidisciplinary care is essential for any child with cancer. This includes involving the child's pediatrician, which will increase and improve the family's support. Such comprehensive care is particularly important for children with other underlying disorders. In addition to WS, other examples include Down syndrome[18] and Charcot-Marie-Tooth disease.[19] For instance, to provide safe and effective care for children with Down syndrome and acute myeloid leukemia, physicians must understand the medical conditions associated with Down syndrome. In addition, patients with Down syndrome may be more sensitive to chemotherapy side effects and in some instances may be treated according to protocols specifically designed for patients with Down syndrome. Patients with Charcot-Marie-Tooth disease, a hereditary motor sensory neuropathy, have increased neurotoxicity with vincristine and methotrexate, and physicians should consider this when planning chemotherapy for patients with this disorder.

This case should serve as a useful example if other children with WS develop a malignancy. Most importantly, children with other multisystem disorders such as Down syndrome, which are associated with a predilection for malignancy and/or increased sensitivity to chemotherapy, will benefit if physicians apply disease-specific guidelines to their care.[20]

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