Cancer Management in Kabuki Syndrome: The First Case of Wilms Tumor and a Literature Review

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Summary: A 3-year-old Japanese girl treated for hypoplastic left heart syndrome and Dandy-Walker syndrome was diagnosed with Kabuki syndrome (KS) with a mutation of *KMT2D*; c.13285C > T: p.Q4429*. Concurrently, macrohematuria portended the diagnosis of Wilms tumor. Postoperative chemotherapy has achieved complete remission despite a prolonged and reduced regimen due to liver dysfunction and convulsions. Cancer predisposition has been suggested for KS due to oncogenic mutations in *KMT2D* or *KDM6A*. The first case of nephroblastoma exemplified the treatability of malignancies in KS patients, as shown in the 9 cases reviewed. Active screening and intervention are recommended for the cure of malignancy in KS children.

Key Words: Kabuki syndrome, nephroblastoma, cancer predisposition, cancer management

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Kabuki syndrome (KS) is a multiple congenital anomaly syndrome, characterized by distinct facial dysmorphism, postnatal growth deficiency, and mild to moderate intellectual disability.[1,2] Affected patients have various complications, such as neurological anomalies, congenital heart disease, endocrine abnormalities, and kidney/ureteral malformation.[3,4] KS is classified into *KMT2D*-associated, autosomal-dominant KS type-1 (MIM# 602113), and *KDM6A*-associated, X-linked-dominant KS type-2 (MIM# 300128). More than half of KS patients have a *KMT2D* mutation, and about 10% of *KMT2D*-negative individuals possess deletions or mutations of *KDM6A*.[3] Recently, genetic screenings for KS have provided useful information about the genotype-phenotype correlations. However, the diagnosis is challenging in newborns and infants.

Wilms tumor (WT) is the most common cancer of the kidneys in children. The current therapeutic strategy has attained a 90% overall survival of patients. Most cases are diagnosed at a median 3 years of age, although bilateral tumors occur earlier in association with congenital syndromes. Syndromic WT was able to be detected through a screening program.[5]

Cancer predisposition has been recently suggested in KS patients, because of 9 reported cases of malignancy[6–13] and the oncogenic potential of the *KMT2D* or *KDM6A* mutations.[14] We herein report the first case of WT in a KS patient and discuss the cancer management for KS children with a review of the literature.

MATERIALS AND METHODS

Whole-exome Sequencing (WES) for the Detection of Germline Mutations

WES was performed in the child and her parents. The DNA was processed with a SureSelect Human All Exon V4 kit (Agilent Technologies Inc., Santa Clara, CA), sequenced on a HiSeq. 2000 (Illumina Inc., San Diego, CA), and analyzed as previously described.[3] The candidate mutations of *KMT2D* were validated by Sanger sequencing.

RESULTS

Patients' Medical Reports

A 3-year-old Japanese female visited us with a complaint of macrohematuria. She had been treated in our hospital for hypoplastic left heart syndrome and Dandy-Walker syndrome. She was born to a healthy mother vaginally at term, weighing 2985 g without any troubles. The patient received anastomosis of both pulmonary arteries for the control of pulmonary artery hypertension and then underwent the Norwood procedure at 9 and 22 days after birth, respectively. Brain magnetic resonance imaging 92 days after birth revealed malformations, including enlargement of the fourth ventricle, a partial defect of the cerebellar vermis, and cyst formation. Under the diagnosis of Dandy-Walker syndrome, ventriculo-peritoneal shunting was conducted at four months of age. Thereafter, she underwent the Glenn procedure and pulmonary angioplasty at 18 months of age. She was awaiting the Fontan procedure on tubal feeding and home oxygen therapy.

On admission, the small chubby girl (height: 83.4 cm [−2.6 SD], weight: 11.4 kg [fifth percentile]), had facial dysmorphism with lower lateral eyelid eversion, arched eyebrows, a depressed nasal tip, and prominent ears. The patient also had hypothyroidism, a duplicated ureter,

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psychomotor retardation of DQ 20, and bilateral hearing difficulty. Her gestalt and accompanied conditions reminded doctors of the potential for a diagnosis of KS until 6 months of age. A cytogenetic study revealed a normal karyotype of 46,XX. WES and Sanger sequencing using peripheral blood mononuclear cell-derived DNA from the patient revealed a heterozygous mutation of c.13285C>T: p.Q4429* in *KMT2D* but no other syndromic gene mutations, including *KDM6A* (Fig. 1A).

Computed tomography (CT) confirmed a demarcated tumor of 5×4.8×4.5 cm (Fig. 1B). The tumor was completely resected. A pathologic study of the tumor determined a mixed-type nephroblastoma without anaplastic nephroblasts (Figs. 1C, D). The diagnosis of stage 1 WT was determined according to the National Wilms Tumor Study classification. Postoperative chemotherapy consisting of vincristine/actinomycin-D was started. However, dose reduction and sufficient intervals between the treatments were required to complete the protocol, because of liver dysfunction (grade 3) and seizures (grade 2). No late effects remained after cancer chemotherapy. She is alive and well and has been in a disease-free state for 18 months since the diagnosis of WT.

Review of the Literature

There have been only 10 KS patients reported who suffered from malignancy, including the present patient (Table 1).[6–13] Eight of them were female. Two developed leukemia or lymphoma, and 8 had solid tumors, including 2 unilateral neuroblastma, and 1 spinal ependymoma. The age at onset was a median of 6 years, ranging from 6 months to 23 years. Three patients carried germline mutations of *KMT2D*. No one had a positive family history for malignancy or anomaly. No parents were diagnosed with KS. Eight patients were alive in the first instance of complete remission, and only 1 died from the progression of synovial sarcoma.

DISCUSSION

The first association of KS and WT was demonstrated in the present patient at 3 years of age. At the first presentation of macrohematuria, she had been treated for hypoplastic left heart syndrome and Dandy-Walker syndrome since the fetal stage. Clinical sequencing is typically delayed in patients with multiple anomaly syndrome, as facial dysmorphism is only noticeable after 6 months of age. Complete remission has continued in the present patient

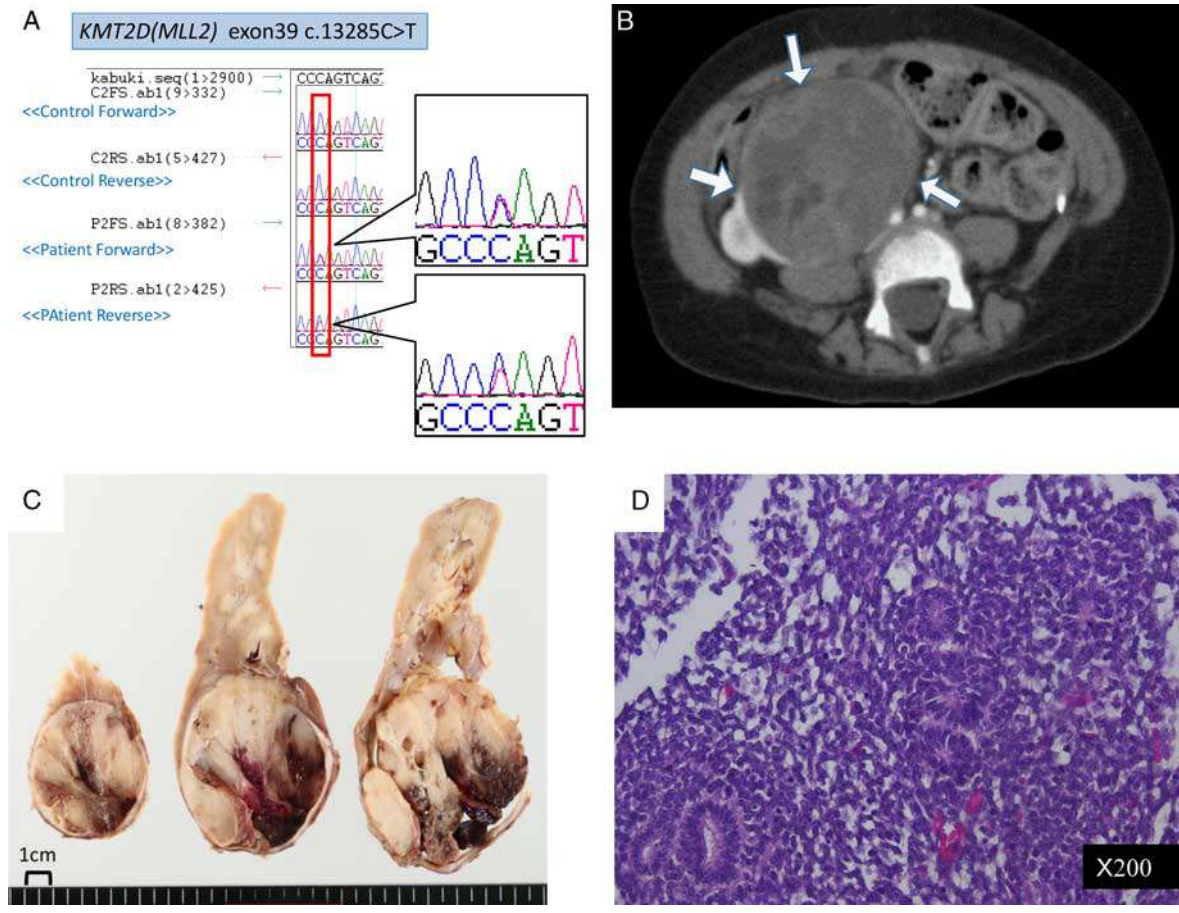

FIGURE 1. A, Whole-exome sequencing and Sanger sequencing using peripheral blood mononuclear cell-derived DNA from the patient revealed a heterozygous mutation of c.13285C>T: p.Q4429* in *KMT2D*. B, A representative image of the abdominal computed tomographic scan on admission. Computed tomography confirmed a well-defined mass of 5×4.8×4.5 cm. The white arrows show the tumor. C and D, A pathologic examination confirmed a mixed-type nephroblastoma without evident anaplastic nephroblasts. B, A photograph of the opened nephrectomy specimen. C, Histopathologic findings of the tumor stained with hematoxylin and eosin (×200). Blastemal and epithelial elements are seen. full color online

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TABLE 1. All Reported Patients With of Kabuki Syndrome Who Developed Malignancy

Patient No.	Age*/ Sex	Genetic Defect *KMT2D*/*KDM6A*	Malignancy†	Treatment	Outcome Observation (mo)	Report
1	6 mo/F	ND	Neuroblastoma (stage 4S)	Observation	Alive (18), CR	Tumino et al[10]
2	ND/F	ND	Neuroblastoma (stage 4)	ND	ND	Merks et al[9]
3	2 y/F	ND	Pre B-ALL	Chemotherapy: ALL-BFM 2000	Alive (14), CR	Scherar et al[6]
4	3 y/M	ND	Burkitt lymphoma (EBV-positive, abdominal)	Chemotherapy	Alive (36), CR	Ijichi et al[7]
5	3 y/F	*KMT2D* c.13285C > T	Wilms tumor (stage 1)	Surgical resection, Chemotherapy	Alive (12), CR	The present case
6	6 y/M	ND	Hepatoblastoma	Chemotherapy: SIOPEL 3	Alive (24), CR	Tumino et al[10]
7	10 y/F	*KMT2D* c.7307_7308insT	Giant cell fibroblastoma (primary: neck, relapse: abdomen)	Surgical resections	Alive (5), CR	Karagianni et al[13]
8	11 y/F	ND	Fibromyxoid sarcoma (low-grade, involved scapula)	Surgical resection	Alive (16), CR	Shahdadpuri et al[8]
9	16 y/F	ND	Synovial sarcoma (lung)	Chemotherapy, Surgical resection, Radiotherapy	Death, relapse	Casanova et al[12]
10	23 y/F	*KMT2D* c.16085_16086delAG	Ependymoma (spinal)	Surgical resection	Alive (14), CR	Roma et al[11]

*The age means the time of the diagnosis of malignancy.
†A patient with EBV-negative Burkitt lymphoma was also recorded, although detailed data on this patient were not recorded at the registration.[17]
ALL indicates acute lymhoblastic leukemia; BFM, Berlin-Frankfurt-Munster; CR, complete remission; EBV, Epstein-Barr virus; F, female; M, male; ND, not described; SIOPEL, Société Internationale d'Oncologie Pédiatrique.

following the optimization of postoperative chemotherapy in light of adverse events. The favorable outcome of WT in this patient and the findings from the literature review may recommend active screening and intervention of malignancy in KS children. The phenotypic variability makes it difficult to diagnose KS in infancy without genetic screening. Life-threatening anomalies in the heart and brain, along with the slow emergence of facial dysmorphism, might have delayed the comprehensive genetic study in our patient.

KMT2D and *KDM6A* defects are reportedly found in 56% to 75% and 5% to 8% of KS patients, respectively.[3,5,15–17] KS has not been recognized as a cancer predisposition syndrome. Given that the estimated incidence of KS is 1 in 32,000 births,[18] the presence of malignancy in 9 KS patients may support a predisposition toward cancer, at least solid tumors, with this syndrome.[6–13] Another concern is the oncogenic potential of *KMT2D* and *KDM6A* defects.[14] The *KMT2D* gene encodes a H3-K4 histone methyltransferase, which forms a complex assembly with other proteins and regulates gene transcription. Somatic mutations in *KMT2D* and *KDM6A* are frequently found in cancer. Homozygous and hemizygous mutations in *KDM6A* have been identified in various types of cancer cells, suggesting that *KDM6A* is a tumor-suppressing gene. However, the female predisposition in KS patients with malignancy suggests a less-causative role of *KMT2D* than *KDM6A* in the case series (Table 1). Further studies are needed to clarify the genetic contribution of germline mutations in *KMT2D* and *KDM6A* to tumorigenesis in KS patients.

Cancer management for KS is a matter of concern. KS is rarely associated with fatal complications that have a negative impact on the life span. Indeed, there are no current studies demonstrating a reduced life expectancy in people who have been diagnosed with KS. Nevertheless, childhood obesity in KS children seems to be associated with cardiovascular risk and diabetes, which have an impact over the life span. Medical intervention may be able to reduce the risks associated with this condition, guaranteeing an average life span for individuals afflicted with this syndrome. In conclusion, the present case and a literature review might support recommendations for proper screening of KS and proactive approaches for the diagnosis of and treatment for malignancy.

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