Kabuki Syndrome with Multiple Associated Surgical Anomalies
(Cleft Palate, Anorectal Anomaly and Diaphragmatic Hernia):
Case Report and Literature Review

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(Received for Publication: October 22, 2015)

Abstract

We report our experience with a case of Kabuki syndrome complicated by multiple anomalies requiring surgery. The patient was a male infant born at 41 weeks 5 days gestation, weighing 4,468 g, who presented with an imperforate anus and cleft palate. A radical operation was performed under a diagnosis of low imperforate anus without fistula. However, an anastomotic leakage occurred, requiring a colostomy. Despite the presence of an asymptomatic concomitant Morgagni hernia, the patient was placed under follow-up observation. Eight months after the infant’s birth, the stoma was closed. Eleven months after birth, Kabuki syndrome was suspected because of the characteristic facial features, and a mutation in MLL2 was diagnosed.

Key words
Kabuki syndrome, cleft palate, anorectal malformation, diaphragmatic hernia

Introduction

In 1981, Niikawa et al. and Kuroki et al. reported a malformation syndrome in individuals presenting with facial features that resemble the makeup of Kabuki actors¹². The five cardinal features of this syndrome include the characteristic facial features, skeletal anomalies, short stature, mental retardation, and characteristic dermatoglyphic patterns. Because of the characteristic facial features, the syndrome has been named Kabuki syndrome (KS). It is an autosomal dominant disorder, and the responsible gene, MLL2 has been reported to be associated with methylation of histones located in region 12 of the long arm of chromosome 12³. We encountered a patient in whom KS was associated with an MLL2 mutation and complicated by a cleft palate, an anorectal malformation, and a diaphragmatic hernia. We report the details of this case and discuss the associated malformations.

Case Report

The case is that of a male who was transferred to our hospital with a cleft plate and an imperforate anus. He had a 39-year-old father, a 28-year-old mother, and two brothers, aged 5 and 3 years. His parents were Chinese citizens. The infant was born at 41 weeks 5 days gestational age, weighing 4,468 g (+3.8 standard deviation [SD]). Cyanosis was noted immediately after birth and oxygen was immediately administered, which resolved the cyanosis. The Apgar scores were 7 at 1 minute and 8 at 5 minutes after birth.

Physical examination on admission showed the following: height, 54.5 cm (+2.6 SD); head circumference, 36.0 cm; body temperature, 36.1°C; respiratory rate, 55 breaths per minute; pulse rate, 140 beats per minute and regular; blood pressure, 76/31 mmHg;
and percutaneous arterial oxygen saturation, 90% to 94% (oxygen 40% via face mask). The infant was of clear consciousness, and his body posture was normal. His muscle tone and movement of his upper and lower limbs were good. Peripheral cyanosis was noted, and congestion of the face was marked. Despite a flat anterior fontanel and large pinnae, the infant’s face did not appear to be characteristic of KS. Although neither labial nor nasal malformation was observed, cleft palate was noted. No thoracic deformity was observed, and no heart murmur was detected. Breath sounds were reduced in the right lung, and transient tachypnea was noted. The abdomen was flat and soft, and no anomaly was observed in the genitilia. An imperforate anus was diagnosed. On the invertogram taken 24 hours after birth, the distance from the blind end of the rectum to the skin was 8 mm, and there was no fistula; thus, a low-type imperforate anus without fistula was diagnosed (Figure 1).

We then performed chest radiography and computed tomography. A mass shadow with a well-defined margin was detected in the medial segment of the right lower lung field (Figure 2–1). Because the liver protruded from the right posterior aspect of the sternum into the thoracic cavity, Morgagni hernia was diagnosed (Figure 2–2). Neither electrocardiography nor echocardiography revealed any abnormalities. On the basis of these findings, a radical perineal operation for the imperforate anus was performed on day 1. Anastomotic leakage occurred on day 7, and a stoma was constructed from the sigmoid colon. The respiratory symptoms had resolved by 24 days, and oxygen administration was discontinued. The infant was discharged at 65 days of age.

Although the infant presented with macrosomia (defined as height >2.6 SD and weight >3.8 SD above the mean at birth), postnatal growth deficiency was observed. By 13 months of age, both height and weight were within the normal range. Motor development was delayed. He was able to sit alone at 10 months, to crawl and to stand while holding onto furniture at 13 months, and to walk alone at 17 months.
At 24 months of age, he was only making sounds and was not able to make clear speech.

The stoma was closed at 8 months after infant’s birth. At 11 months after birth, he was diagnosed as having KS because of his peculiar facial features (characterized by long palpebral fissures with eversion of the lateral third of the lower eyelids, a broad and depressed nasal tip, arched eyebrows, strabismus of the left eye, and large prominent earlobes) (MLL2 mutation: c.3532C>T). He currently defecates easily without the use of laxatives or enemas. Imaging studies show no worsening of the Morgagni hernia, and he does not currently have any clinical symptoms. Thus, he has been placed under follow-up observation.

Discussion

Although approximately 400 cases of KS have been reported in Japan and overseas59,10, the prevalence is estimated to be 1/32,00010. Most are isolated cases, and there are only a few reports of familial occurrence59. The gene identified as responsible are MLL23) and KDM6A3), and a molecular genetic test for MLL2 is clinically available. The MLL2 gene mutation has been found in 61.7% and the KDM6A gene mutation in 6.2% of patients clinically diagnosed as having KS7). Because MLL2 and KDM6A are histone methyltransferases for H3K4 and H3K27, respectively, KS appears to be related to aberrant histone methylation. In our case, a MLL2 abnormality was noted due to the characteristic facial features, which lead to a definitive diagnosis 11 months after birth.

The five cardinal features of KS and their frequencies are as follows: (1) characteristic facial features (observed in up to 100% of patients), which include long palpebral fissures with eversion of the lateral third of the lower eyelids (in almost 100%), arched eyebrows, of which the lateral half is sparse, a broad and depressed nasal tip, short nasal septum, and large prominent earlobes; (2) skeletal abnormalities (observed in up to 92%) including brachydactyly (especially shortening of the little finger and the middle phalanx), scoliosis, sagittal cleft of the vertebral bodies, and rib anomalies; (3) specific dermatoglyphic patterns (observed in up to 90%); (4) mental retardation (observed in up to 92%); and (5) short stature (postnatal growth deficiency) (observed in up to 88%). The diagnosis is initially made on the basis of clinical findings, although first KS is suspected because of the characteristic facial features.

The malformations associated with KS that have been reported including congenital heart defects; renal and genitourinary anomalies; cleft lip and/or cleft palate; digestive tract defects including anorectal malformation, blepharoptosis and strabismus; widely spaced teeth, and dental hypoplasia. Functional abnormalities include susceptibility to infection, autoimmune disease, convulsions, endocrine abnormalities (including early breast development in girls), eating problems, and hearing impairment. The associated malformations observed in our case were cleft palate, anorectal malformation, and diaphragmatic hernia (i.e., Morgagni hernia). The prevalence of a combination of KS and cleft palate is high, at 35% among the patients with KS4), half of those with this combination present with an MLL2 gene mutation7). A combination of KS and anorectal malformation has been reported in 9 patients8–12) including ours, as shown in Table 1, and the prevalence of this combination is reported to range from 5% to 25%).13,14,15 Interestingly, all of these patients except ours were girls, all of whom had a vestibular fistula and many of whom had a cleft palate (6/9). Postoperative bowel function appears to be good in them.

A combination of KS and diaphragmatic hernia has been reported in 8 cases including ours, as shown in Table 212,13–15). Half of them appear to be characterized by Morgagni hernia. Moreover, the diaphragmatic hernia in 2 other cases was located on the right side. Although a combination of KS and diaphragmatic hernia has been considered rare, the prevalence of this combination might be higher than we expect. When we focused on a combination of KS and other diaphragm diseases in addition to diaphragmatic hernia, we unexpectedly found more cases with concomitant diaphragmatic evagination. One report even noted an incidence of such cases of 25%.15,16 From the literature review, we identified 12 cases9,12,13,15–26. Diaphragmatic evagination occurred on the right side in 78% (7/9) and on both sides with right-side predominance in 22% (2/9). In addition, among the 8 cases involving a diaphragmatic hernia, Table 2, 6 lesions were located on the right side, including the 4 Morgagni hernias; the location was unknown in 2 cases (cases 5 and 7). The overwhelming predominance on the right side is interesting. Moreover, all patients with concomitant diaphragmatic anomalies survived, so the combination of KS and diaphragmatic defect does not appear to determine prognosis.

The reason for the presence of multiple associated malformations, as seen in our case, remains unknown. However, because KS is complicated by vari-
ous malformations, the *MLL2* mutation is assumed to affect multiple genes in multiple organs. In addition, the KS complicated by cleft palate, anorectal malformation, and diaphragmatic hernia in our patient did not appear to be a life-threatening problem.

**Conflict of Interest**

The authors declare that they have no conflicts of interest.

### Table 1. Kabuki Syndrome Associated with Anorectal Anomalies

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Main manifestations</th>
<th>Anorectal anomaly</th>
<th>Associated abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;3&lt;/sup&gt;</td>
<td>9 y</td>
<td>F</td>
<td>+ + + ± ±</td>
<td>VF</td>
<td>Cleft palate, ASD, webbed neck, renal anomaly, long great toes</td>
</tr>
<tr>
<td>2&lt;sup&gt;3&lt;/sup&gt;</td>
<td>6 y</td>
<td>F</td>
<td>+ + + + +</td>
<td>VF</td>
<td>Cleft palate, VSD, aortic aneurysm, horseshoe kidney, bifid pelvis, pigmented retina, abnormal electroencephalogram</td>
</tr>
<tr>
<td>3&lt;sup&gt;3&lt;/sup&gt;</td>
<td>4 y</td>
<td>F</td>
<td>+ - - + ±</td>
<td>VF</td>
<td>Autism, retarded bone age</td>
</tr>
<tr>
<td>4&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3 y</td>
<td>F</td>
<td>+ - - + ±</td>
<td>VF</td>
<td>Right renal agenesis, congenital hip dislocation, retarded bone age, rhVSD</td>
</tr>
<tr>
<td>5&lt;sup&gt;3&lt;/sup&gt;</td>
<td>9 y</td>
<td>F</td>
<td>+ + + + +</td>
<td>Imperforate anus</td>
<td>Premature breast development, bilateral dislocated hearing loss, cleft palate</td>
</tr>
<tr>
<td>6&lt;sup&gt;10&lt;/sup&gt;</td>
<td>16 y</td>
<td>F</td>
<td>+ + + + +</td>
<td>VF</td>
<td>Cleft palate, ectopic right kidney, VUR</td>
</tr>
<tr>
<td>7&lt;sup&gt;11&lt;/sup&gt;</td>
<td>13 y</td>
<td>F</td>
<td>+ + + + +</td>
<td>VF</td>
<td>Single umbilical artery, biliary atresia</td>
</tr>
<tr>
<td>8&lt;sup&gt;12&lt;/sup&gt;</td>
<td>2 y</td>
<td>F</td>
<td>+ + + + +</td>
<td>VF</td>
<td>Cleft palate, lower lip pits, hypopigmentation, diaphragmatic hernia, hypogammaglobulinemia, early breast development, ASD, VSD, GERD</td>
</tr>
<tr>
<td>present</td>
<td>7 mo</td>
<td>M</td>
<td>+ + +</td>
<td>Imperforate anus without fistula (low)</td>
<td>Cleft palate, Morgagni hernia, hypoglycemia (neonatal)</td>
</tr>
</tbody>
</table>

A: characteristic facial features, B: skeletal abnormalities, C: specific dermatoglyphic patterns, D: mild to moderate mental retardation, E: postnatal growth deficiency

VF: vestibular fistula

### Table 2. Kabuki Syndrome Associated with Diaphragmatic Defects

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Main manifestations</th>
<th>Diaphragmatic anomaly</th>
<th>Associated abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;15&lt;/sup&gt;</td>
<td>2 y</td>
<td>F</td>
<td>+ + + + + +</td>
<td>Morgagni</td>
<td>Coelacation, ASD, cleft palate, early breast development</td>
</tr>
<tr>
<td>2&lt;sup&gt;16&lt;/sup&gt;</td>
<td>15 y</td>
<td>F</td>
<td>+ + + + + +</td>
<td>Morgagni</td>
<td>Coelacation, hypertrophic pyloric stenosis, GERD, bronchomalacia, abnormal right bronchial tree</td>
</tr>
<tr>
<td>3&lt;sup&gt;17&lt;/sup&gt;</td>
<td>3 y</td>
<td>M</td>
<td>+ + - + +</td>
<td>Morgagni</td>
<td>Coelacation, hypertrophic pyloric stenosis, GERD, bronchomalacia, abnormal right bronchial tree</td>
</tr>
<tr>
<td>4&lt;sup&gt;18&lt;/sup&gt;</td>
<td>N</td>
<td>F</td>
<td>+ + + + + +</td>
<td>DD</td>
<td>Double collecting system of the right kidney</td>
</tr>
<tr>
<td>5&lt;sup&gt;18&lt;/sup&gt;</td>
<td>N</td>
<td>M</td>
<td>+ + + + + +</td>
<td>Right CDH</td>
<td>CHARGE association</td>
</tr>
<tr>
<td>6&lt;sup&gt;18&lt;/sup&gt;</td>
<td>N</td>
<td>F</td>
<td>+ + + + + +</td>
<td>DD</td>
<td>Cleft palate, bifid tongue, ASD, right kidney duplication, vermis atrophy</td>
</tr>
<tr>
<td>7&lt;sup&gt;12&lt;/sup&gt;</td>
<td>2 y</td>
<td>F</td>
<td>+ + + + + +</td>
<td>Right CDH</td>
<td>Cleft palate, lower lip pits, hypopigmentation, anorectal anomaly, hypogammaglobulinemia, early breast development, ASD, VSD, GERD</td>
</tr>
<tr>
<td>present</td>
<td>7 mo</td>
<td>M</td>
<td>+ +</td>
<td>Morgagni</td>
<td>Cleft palate, anorectal anomaly, hypoglycemia (neonatal)</td>
</tr>
</tbody>
</table>

A: characteristic facial features, B: skeletal abnormalities, C: specific dermatoglyphic patterns, D: mild to moderate mental retardation, E: postnatal growth deficiency

DD: diaphragmatic defect, CDH: congenital diaphragmatic hernia

### References


2) Kuroki Y, Suzuki Y, Chyo H, Hata A, Matsui I. A new malformation syndrome of long palpe-


