CLINICAL QUIZ (p54) ANSWER

What is the diagnosis?

The clinical diagnosis of our patient is Kabuki syndrome (KS). Molecular testing showed there is a heterozygous nonsense mutation (Gln3892*) in exon 39 of *KMT2D* {NM_003482.3} gene that confirmed clinical diagnosis.

KS was first reported in 1981 by Japanese paediatrician Niikawa and Kuroki.[1]

There are 5 cardinal features of KS as defined by Niikawa,[1] including typical 1) facial features, 2) skeletal anomalies like brachydactyly, 3) persistent finger pads, 4) mild to moderate intellectual disability and 5) postnatal growth deficiency.

Other common manifestations of KS included feeding difficulties (70%), congenital heart defect like septal defect and coarctation of the aorta (40-50%), joint hypermobility (50-75%) and hypotonia (25-89%).[2]

The typical distinctive facial features of KS had been described in the literature Included long palpebral fissures with eversion of the lateral one third of the lower eyelid, arching eyebrows with lateral part being broad and sparse, dense eyelashes. The columella is short and bulbous nasal tip is depressed resulting in triangular nostrils. Ears are large, prominent and cupped. Ocular hypertelorism may also be observed.[1]

What is the molecular defect and clinical features in KS?

Currently there are 2 genes being associated with KS. KS type 1, the more common type of KS which accounts for 56-75% of all the Kabuki cases,[3] is an autosomal dominant disease caused by mutation of *KMT2D* gene. *KMT2D* gene is located at chromosome 12q13.12.[4] It encodes MLL2 protein, also named as H3K4 methyltransferase, which regulates the methylation of histone 3 lysine 4. This affects the action of euchromatin which in turn disturbs active transcription.[3] The mutation is most frequently due to nonsense (36.5%), deletion/duplication (33.2%) and missense (21.6%) mutations and results in loss of function of MLL2 protein.[3]

Type 2 KS is the result of *KDM6A* gene mutation which is located at chromosome Xp11.3.[4] The *KDM6A* gene mutation accounts for 5-8% of all causes of KS.[3] The gene codes for H3K27 demethylase which is responsible for the activation of chromatin by erasing repressive polycomb-derived methylation marks and deposition of activating H3K4 methylation mark on chromatin. These allow the recruitment of RNA polymerase II complex.[3] Haploinsufficiency of the protein is attributed to the deletion (25%), nonsense (28.5%) or missense (21.9%) mutation of the gene.[3]

The prevalence of different symptoms in *MLL2 (KMT2D*) and non-*MLL2* mutations is demonstrated in Table 1.

What is the diagnostic criteria for KS?

There is no universal clinical diagnostic criteria established for KS. The diagnosis is mainly based on clinical features. Scoring system has been proposed to enhance clinical diagnosis and to predict the *KMT2D* gene mutation (Table 2). Based on 6 different features, the likelihood of having *KMT2D* gene mutation is assessed. With the maximum score of 10, the higher the score, the greater the chance of getting the gene mutation. The mean score for those patients with *KMT2D* gene variant is 6.1 while those without the gene variant obtain 4.5 points.[5]

What is the management of KS?

The management for KS is mainly supportive and symptomatic (Table 3).

Table 1 Compare the prevalence of symptoms between *MLL2* and non-*MLL2* mutations[5-8]

Clinical features	*MLL2* mutation (%)	Non-*MLL 2* mutation (%)
Flat nasal tip	60.0-85.3	23.3-45.5
Intellectual disability	52.2	29.0
Arched eyebrows	53.8-85.3	24.6-45.5
Broad nasal root	44.6-85.3	15.5-45.5
Thin upper and full lower lips	52.5-85.3	23.7-45.5
Short stature	39.7-44.74	17.5-100.0
Lax joint	32.5-50.8	8.70-24.6
Blue sclera	23.3	6.7
Frequent infection	39.7-64.1	14.3-42.4
Large dysplastic ears	48.5	30.9
Hypotonia	47.5- 86.49	0.0-32.2

Table 2 Kabuki syndrome phenotype scoring system (*KMT2D* gene mutation)[5]

Phenotypic finding	Details	Score
Facial features	- Eye: long palpebral fissures, everted lower eyelids, arched eyebrows with lateral one third being sparse, strabismus, blue sclera, ptosis - Ear: prominent unfold cupped ears - Nose: flat nasal tip, board nasal root - Teeth: abnormal dentition, oligodontia - Others: high/cleft palate, micrognathia, thin upper and full lower lips, lip nodules	1-5*
Limb features	- Persistent fetal pads - Brachydactyly or clindactyly - Lax joints - Hip dislocation	0-1**
Microcephaly		1
Short stature		1
Heart		1
Kidney		1
Total		0-10

*0-3 features=1 point; 4-6 features=2 points; 7-9 features=3 points; 10-12 features=4 points; 13-15 features=5 points

**0-1 features=0 point; 2-4 features=1 point

Table 3 The management for KS is mainly supportive and symptomatic[4]

KS features	Investigation and management
Feeding problem	24 pH probe and barium swallow if indicated.
Gastro-esophageal reflux	Gastrostomy tube replacement may be necessary
Seizure	Electroencephalogram for clinical seizure
Hormone deficiency	Endocrine assessment like baseline hormonal level (thyroid function and growth hormone)
Congenital heart problem	Baseline cardiac evaluation
Congenital renal problem	Baseline renal ultrasound
Eye problem e.g. myopia	Annual eye assessment
Hearing	Annual hearing assessment Hearing aid or even tympanostomy tube placement may be required
Immune deficiency	T cell count and immunoglobin level
Short stature	Monitor growth rate by specific growth chart
Developmental delay	Developmental evaluation and appropriate training

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References

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