Clinical Immunology 207 (2019) 55–57

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Exome sequencing confirms diagnosis of kabuki syndrome in an-adult with hodgkin lymphoma and unusually severe multisystem phenotype

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ABSTRACT

We report a 34-year-old male patient with a novel variant in *KMT2D* gene, which finally ended a quest for a diagnosis that was clinically suspected in the past, prior the molecular basis of Kabuki Syndrome (KS) was known. The patient showcases the multisystemic features, with involvement of all previously associated with KS body systems, presence of immune deficiency as well as autoimmune disorders, requiring three pancreatic transplants. We also report, for the first time to our knowledge, the presence of epidural lipomatosis and Hodgkin Lymphoma in a patient with KS.

1. Introduction

Kabuki Syndrome (KS), named after the make-up of Kabuki actors in Japan, was first described in 1981 in two case reports of five Japanese patients each [1,2]. The predominant features of this syndrome are 1) distinctive facial features, such as eversion of the lateral lower eyelid, long palpebral fissure, arched and sparse lateral third eyebrows; 2) skeletal abnormalities; 3) dermatoglyphic abnormalities, such as persistence of fetal fingertip pads; 4) mild to moderate intellectual disability; and 5) post-natal growth deficiency [3]. It is an autosomal dominant disorder with an estimated incidence of 1 in 32,000 [3], caused by loss of function variants. The most frequent variants (56–75%) are reported in *KMT2D* or *MLL2* [4,5], *KDM6A* accounting for 5–8% [6,7] of KS patients, and other genes, including *RAP1A, RAP1B* [8] accounting for smaller proportions. This report highlights the phenotypic heterogeneity in KS and reports for the first time to our knowledge, Hodgkin Lymphoma and epidural lipomatosis in a patient with KS.

2. Clinical report

The patient was born via induced vaginal delivery at 37 weeks of gestation, weighing 7.5 pounds. Maternal hypertension and first trimester bleeding complicated the pregnancy. Bilateral clubfeet, hirsutism, hypotonia and feeding problems were noted at birth.

As an infant, he had recurrent ear infections and multiple GI problems. At 15 months he underwent pyloroplasty for peptic ulcer disease and at age 4 years Billroth II procedure. Both gross and fine motor skills were impaired, with first steps at 16 months. He had failure to thrive from 4 years to 17 years and was on total parenteral nutrition (TPN). Colonoscopy at around age 18 demonstrated diffuse inflammatory changes and he was treated with Remicade 1.5 mg/kg every six weeks. Remicade was discontinued three years later due to a lack of evidence of inflammatory changes during GI investigations done at that time. At the request of the family for relief from chronic diarrhea and to facilitate independence from TPN, Remicade was reinstituted at 7 mg/kg every 8 weeks at the age of 25. Although an extensive evaluation had not shown evidence of Crohn's disease, the patient had an improvement and TPN was discontinued.

He had IgA and IgG deficiencies, and has been treated with IVIG

Abbreviations: COMPASS, Complex Of Proteins Associated with Set1; CVID, Combined Variable Immuodeficiency; FISH, Florescent In situ Hybridization; GAD65, Glutamic Acid Decarboxylase; GI, GastroIntestinal; IVIg, Intravenous IgG; *KDM6A*, Lysine Demethylase 6A; *KMT2D*, Lysine Methyltransferase 2D; MRI, magnetic resonance imaging; *RAP1A*, Ras related Protein 1A; *RAP1B*, Ras related Protein 1B; T1D, Type 1 Diabetes Mellitus; TPN, Total parenteral nutrition

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https://doi.org/10.1016/j.clim.2018.09.013
Received 29 November 2017; Received in revised form 19 August 2018; Accepted 28 September 2018
Available online 30 September 2018
1521-6616/

since age 2. He was diagnosed with Combined Variable Immunodeficiency (CVID) at age 4.

Diabetes mellitus Type 1 (T1D) was diagnosed at 8 years and insulin therapy initiated. The patient struggled to maintain good control over his T1D, given his dumping syndrome post Billroth and dependence on TPN. He was also placed on pancreatic enzyme replacement, but subsequently recommended for pancreatic transplant (PT). He underwent three pancreatic transplants at ages 21, 22 and 32. The first two transplants failed owing to early arterial thrombosis after the first transplant, and intra-abdominal hemorrhage complicated with portal vein thrombosis after the second. The patient received induction with Thymoglobulin and Prednisone (5 doses at 1.5 mg/kg body weight on days 0–4 after transplantation, 60 mg prednisone on day 0 and 30 mg on days 1–4) and maintenance immunosuppression consisting of Tacrolimus (Tac), mycophenolate Mofetil (MMF) and Prednisone. The doses of TAC and MMF were guided by serum concentration testing, Prednisone rapidly tapered to 5 mg/day by week 12. The 12 weeks of Prednisone at supra physiologic dose only occurred with the third PT: the current functioning transplant. Recurrent failed transplantation resulted in the development of anti-HLA antibodies delaying the third transplant. Subsequent to the third pancreatic transplant, the patient developed EBV positive Hodgkin Lymphoma. He underwent six cycles of ABVD chemotherapy regimen and was in a complete remission.

Extensive thoracic epidural lipomatosis was noted on spine MRI during a neurological evaluation when the patient was 24 years old. The patient underwent T5 through T9 decompressive laminectomy and removal of epidural lipomatosis for progressive thoracic myelopathy at the age 32.

The patient has left sided hearing loss and uses a hearing aid. He also has spinal stenosis, progressive myopia, easy bruising, iron and Magnesium deficiencies, sleep apnea, hypersomnolence, gynecomastia, and a large tongue.

The patient first saw a Medical Geneticist at the age 13, when possibility of KS was raised. The genetic cause of KS was unknown at that time. Subsequently, at the age 20, he was evaluated by another geneticist who agreed that patient had features associated with KS. He had negative karyotype and subtelomeric FISH, available then genetic testing options.

During his most recent evaluation in genetics, the previously noted history and physical findings were corroborated in addition to long palpebral fissures, long eyelashes, ptosis, arched but not sparse eyebrows, joint hypermobility mostly of upper extremities and pes planus. Diagnosis of KS was once again considered but given the complex medical history, a chromosomal microarray followed by whole exome sequencing were suggested.

3. Cytogenetic and molecular genetic testing

The chromosomal microarray was normal. Whole Exome Sequencing reported a de novo novel heterozygous nonsense variant in the *KMT2D* gene (NM_003482.3), c.12985C > T, p.Gln4329*, confirming the diagnosis of Kabuki Syndrome in this patient. No other variants relevant to the phenotype were identified.

4. Discussion

Although first described in the 1980s [1–3], it was only in 2010 that the first causative gene for KS was identified [9]. Majority of KS patients present with the typical facial features [10], but in our case, two of the major facial findings, lower eyelid eversion and sparse eyebrows were conspicuously missing. About 6% of *KMT2D* variant positive patients have been reported without typical facial features [11]. It should be noted these facial features are difficult to identify in some patients regardless of age.

Immune dysfunction has been associated with KS [12–15] and most patients have been shown to have low IgA as well as IgG levels. In our patient measurements since the age of 20 years showed persistently normal IgG levels as expected with ongoing IVIG therapy, low IgA levels and IgM levels were fluctuating between low and normal (Table 1). In a review of immunoglobulin levels in 19 patients [16], only one patient was found to have low IgA and IgM, with normal IgG levels. Low immunoglobulin levels in KS mimic CVID and as in our case, may warrant monitoring immunoglobulin levels and IVIG therapy in patients with KS.

Table 1
Levels of IgA, IgM and IgG in this patient in a span of 14 years.

	IgA (mg/dL)	IgM (mg/dL)	IgG (mg/dL)
Normal range	61–356 mg/dL	37-286 mg/dL	767-1590 mg/dL
Age: 20	17	149	823
Age: 22	17	51	952
Age: 24	15	23	1090
Age: 27	10	57	1110
Age: 29	12	130	1220
Age: 31	11	24	1190
Age: 34	19	27	1200

Autoimmune conditions including hemolytic anemia, idiopathic thrombocytopenic purpura thyroiditis and vitiligo [17] have been described in KS. Although early onset T1D has been previously reported in KS at the age of 18 years [18], our patient had TID since age 8, and a persistently low $CD19^+$ B-cell count since the age of 20 years (Table 2).

Although T1D is traditionally considered to be mediated by a T-cell autoimmune reaction to islet antigens, the role of islet reactive B-cells is gaining evidence, promoting autoimmunity by a number of mechanisms like antigen presentation, autoantibody production and release of pro-inflammatory cytokines [19] (Table 2). The patient tested positive for Glutamic Acid Decarboxylase 65 antibody (GAD65 Ab) but the titers were low (0.10 nmol/L) and this test result may have to be interpreted with caution in the context of regular IVIG therapy and immunosuppression. Immune suppression may also be the cause of the low B-cell counts. Further investigations into development of T1D in patients with KS are required to delineate the pathophysiological mechanism.

In a recent review [20] of KS patients presenting with tumors it was noted that the association of KS with tumor predisposition might be underreported. Hematological malignancies are rare in KS, and Hodgkin Lymphoma has not been reported to our knowledge. *KMT2D* is one of the most frequently mutated genes in Follicular lymphomas (FL) and Diffuse Large B cell Lymphomas (DLBCL) [21]. There is recent evidence that disruption of *KMT2D* promotes lymphomagenesis by diminished global methylation in germinal center B-cells [22]. *KMT2D* encodes the catalytic domain for the COMPASS (Complex Of Proteins Associated with Set1) complex. This complex facilitates transcription through mono- and di-methylation of histone 3 lysine 4 (H3K4) at enhancer regions in DNA. Truncating mutations of the protein will cause loss of enzymatic activity leading to haplo-insufficiency. Although most tumor suppressor genes have bi-allelic mutations, many cases (25%) of FL and DLBCL are known to retain a wild type allele, indicating that *KMT2D* haploinsufficiency may be enough for malignant transformation [22]. KMT2D has been proposed as a novel driver gene for acute lymphoblastic leukemia in a series of children [23] and also as a tumor suppressor gene which integrates in physiological B cell signaling pathways and is found mutated in human lymphomas.

The overlapping roles of *KMT2D* in immune regulation via B-cell terminal differentiation [24] and germinal center B-cell proliferation can be speculated to play a part in the development of Hodgkin Lymphoma in this patient. To our knowledge, two case reports [25,26] have reported kidney transplantation in Kabuki syndrome patients, neither of these patients developed lymphoma post-surgery to date based on literature search. In our own experience with pancreas transplants in over 250 patients, we have not encountered post-transplant development of

Table 2
Levels of T, B, and NK cells measured for this patient in a span of 14 years.

	%CD19 B cells	%CD16 + CD56 NK cells	%CD3 T cells	%CD4 T cells	%CD8 T cells
Normal range	7–24%	4–28%	58–86%	32–64%	15–40%
Age: 20, 2 days prior to transplant	16	6	76	54	17
Age: 22, 10 days prior to transplant	10	7	83	48	26
Age: 24	2	13	85	26	56
Age: 27	4	6	89	47	39
Age: 29	6	4	89	42	42
Age: 31	3	6	90	37	46
Age: 34	4	6	89	40	45

Hodgkin Lymphoma. Our patient also has thoracic epidural lipomatosis that is not yet reported in the literature in association with KS, although there was evidence of ocular lipoma [27]. On the other hand, the possibility that immune suppression may have played a role in the development of both, the Hodgkin lymphoma and the epidural lipomatosis, cannot be eliminated in this case.

This report recounts the history of KS through a patient whose condition occurred before the genes for Kabuki Syndrome were elucidated, and demonstrates the power of next generation sequencing to provide genetic diagnoses in patients with long lasting diagnostic dilemmas. Although type 1 diabetes, inflammatory bowel disease [28], and exocrine pancreatic insufficiency have been reported before in Kabuki Syndrome, our case is unusual for its severity and very early onset of these disorders. To our knowledge this is the first report of a KS patient with Hodgkin lymphoma and epidural lipomatosis as well as the first case of KS patient to receive a pancreatic transplant alone. These could be related to the disease and extended lifespan facilitated by currently available therapies, or as side effects of those therapies. Differentiating causality for these phenotypes are challenges for the future.

Acknowledgement

We acknowledge the patient and their family for their participation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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