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CASE REPORT

Autoimmune hemolytic anemia in a patient with Kabuki Syndrome - a case report in São Paulo and a brief discussion about Kabuki Syndrome and association with autoimmunity

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Abstract

Kabuki syndrome (KS), first described in Japan in 1981, is a rare disease characterized by a peculiar facies, postnatal growth de?ciency, intellectual disability and a set of malformations, such as skeletal and visceral abnormalities. In the natural history of KS, abnormal immune events are presents and this case report contribute with the understanding and consolidation of hematologic autoimmune desorders. This article describes a case report of a patient with previous diagnosis of Kabuki syndrome with a autoimmune hemolytic anemia in a hospital of São Paulo, with adequate response and resolution with corticosteroids terapy. The article also makes as a brief explanation of correlation with autoimmunity, immunodeficiency and Kabuki syndrome.

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INTRODUCTION

The Kabuki Syndrome (KS), first described in Japan in 1981, is a rare disease characterized by peculiar facies, postnatal growth deficiency, intellectual disability and a set of malformations, such as skeletal and visceral abnormalities[1,2]. KS presents a strong clinical and biological heterogeneity, with rare and diverse symptoms (endocrine abnormalities, autoimmune disorders, obesity, etc.), being considered a systemic disorder[3,4,5].

The incidence of KS is about 1/32,000 live births. Regarding the correlated genetic mutations, those of the mixed lineage leukemia gene 2, KMT2D (formerly MLL2) mapped on chromosome 12q[13,12], are described in 55-80% of patients with KS[1,2]. KMT2D is a histone H3 lysine 4 (H3K4)-specific methyltransferase that belongs to the SET1 family of the human SET domain methyltransferase protein superfamily. While mutations in the KMT2D complex have been identified in most patients with KS, some patients have mutations in the KDM6A, a demethylase responsible for removing methylation tags derived from the regressive Polycomb complex. Currently, some genetic subtypes of KS have been identified: autosomal dominant KS type 1 associated with KMT2D and X-linked dominant KS associated with KDM6A type 2[10,11].

Although some of these genetic alterations are already known and have been described, other potential genetic defects remain unknown in about 30%[1]. In the natural history of KS, abnormal immune events are present and this case report aims to contribute to the understanding and consolidation of autoimmune disorders, especially the hematological ones, correlated with the syndrome.

CASE REPORT

The patient in this case is male and is eleven years old, he has been on follow up with the medical genetics service since he was seven years of age, with clinical-laboratory diagnosis of Kabuki Syndrome (KS) and genetic examination with detection of mutation in the MLL2 gene (KMT2D), often described as one of the anomalies that causes this pathology. Within the past pathological history, he had recurrent pneumonia in the first year of life, recurrent acute otitis media, with tympanostomy at six years of age, surgical correction of hiatal hernia and gastroesophageal reflux disease at two years of life, and multiple hospitalizations for bronchiolitis. At no time did the patient require admission to an intensive care environment.

Among the phenotypic alterations that are characteristic of KS, the patient had an oblique and upward-slanting palpebral fissure, intellectual disability, delayed neuropsychomotor development and mild weight and stature, a short and bubbly nose, short philtrum, spaced teeth, in addition to orthopedic alterations such as clinodactyly in 4th and 5th bilateral fingers, brachydactyly and thoracic kyphosis.

In a previous request for immunophenotyping of T, B and NK lymphocytes, immunoglobulin dosage, autoantibody research (anti-thyroglobulin, anti-peroxidase, isohemagglutinin and direct antiglobulin test) and vaccine response, requested three years before the event, there were no notable abnormalities. In the last hematological exams performed one year before the case, there were no relevant changes.

At eleven years of age, the patient presented to the pediatric emergency room in the state of São Paulo with an acute complaint of progressive jaundice, choluria, adynamia and anorexia; he had no fever, no use of recent medication or vaccination, no bleeding or bruising, as well as no previous similar episodes. Upon physical examination, he presented with moderate jaundice, moderate to severe pallor, no signs of hemodynamic instability and no palpable visceromegaly.

His workup performed upon admission, showed high total bilirubin (7.21mg/dL) with predominance of indirect bilirubin (6.89mg/dL), hemoglobin of 5g/dL, hematocrit of 17.6%, MCV of 112.1 fl, HCM 31.8 pg, CHCM 28.4 g/Dl, RDW 31.6 %, target-like red blood cells and schizocytes in the peripheral smear, leukocytes: 18480/mm³ with 2% myelocytes, 2% metamyelocytes, 4% rods and 49% segmented, reticulocytes 37.8% (654,100/mm³), no thrombocytopenia (platelets 229,000/mm³), increased LDH at 1536U/L, high total reticulocytes? 654,000, normal serum iron, increased transferrin saturation (71 %), positive direct coombs, with indeterminate IgG positive irregular antibody test; examinations relating to both renal and hepatic function were normal. Serology for infectious diseases, such as acute viral hepatitis and mono-like syndromes were negative.

In consultation with the pediatric hematology team, a diagnostic hypothesis of autoimmune hemolytic anemia was performed and pulse therapy with methylprednisolone 30mg/kg/day for 3 days was indicated. The patient evolved with significant clinical and laboratory improvement, presenting hemoglobin of 7.7g/dL, hematocrit of 26%, maintaining mild macrocytosis, anisocytosis and evident polychromasia, RDW 26.6% white series similar to the previous exam, reticulocytes 37%/900,000/mm³, DHL 1303U/L, with a drop in total bilirubin to 4.43mg/dL and indirect bilirubin to 3.85md/dL, without other relevant laboratory alterations after having used prednisolone. Hospital discharge took place five days after admission, with early return to pediatric hematology outpatient clinics.

The patient was discharged five days after admission, with instructions to return to an outpatient clinic of pediatric hematology and adequate long-term clinical follow-up. Subsequently, the patient continued to use prednisolone for about two months, evolving with hematimetric levels similar to those previously mentioned.

DISCUSSION

KS is a rare syndrome with multiple anomalies. In 2010, KMT2D was identified as the first gene causing it. Based on published reports, 55-80% of KS cases can be explained by mutations in this gene. This syndrome is associated with autoimmune and hematologic abnormalities, mainly idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia, leukoplakia, vitiligo, and thyroiditis[1,3].

According to previous publications and reports, KS-associated autoimmune cytopenia usually have a chronic, relapsing course. Conventional therapy (intravenous immunoglobulins and corticosteroids) of these conditions is often marked by a lack of autoimmunity response and/or therapy side effects.[3,4]

Some studies have found a high prevalence of immunological manifestations in KS and in some reported studies, the incidence of autoimmune manifestations was 25.6% in adults afflicted with KS, compared to 7.6 to 9.4% in the adult population in general[4,5,6].

Idiopathic thrombocytopenic purpura (ITP) is rare in the general population, with an overall incidence of less than 1/10,000, while more than 20 cases in KS patients have been described to date. Furthermore, in several of them, ITP had a more severe chronic or relapsing course and, in some patients, it was complicated by pancytopenia. In at least four patients, this comorbidity was considered life-threatening, poorly controlled by conventional therapy, and required splenectomy or anti-CD20 monoclonal antibody[8,9,10].

KS is also characterized by immune dysfunction. Such patients are at increased risk of recurrent otitis media due to lack of antibodies, loss of memory cells, and poor response to the vaccine. Abnormalities regarding immunoglobulins such as hypogammaglobulinemia with IgA deficiency are found as well as terminal B cell mal differentiation, which will further result in humoral immunodeficiency and autoimmunity. Both mechanisms may explain recurrent bacterial respiratory infections, especially otitis and pneumonia in patients with KS[1,5].

The lack of opportunistic or complicated viral infections indicates that severe T and/or NK cell defects are not part of the syndrome. In a cohort of KS patients from Brazil, four out of seven patients were reported to have allergic manifestations (three rhinitis and one asthma, accompanied in three cases by atopic dermatitis)[5]. Due to the similarity of the immunological defects in KS and the common variable disorders of immunodeficiency or common variable immunodeficiency (CVID), it is possible that immunoglobulin levels in a child with KS may initially be normal but later become abnormal. The rate of any autoimmune disease in KS subjects with IDCV was 28% versus 9% without immunological manifestations. This observation is related to the fact that IDCV is often associated with AID in the literature, which led us to suppose that KS individuals with IDCV should be supervised even more carefully for autoimmune manifestations[4,6,8].

Our patient developed autoimmune hemolytic anemia and showed significant improvement with corticosteroids. Previous tests for screening for autoimmune diseases were negative just a few years before their occurrence, which supports the idea that such morbidities can occur even later in childhood, and hematological and immunological evaluations should be performed serially to diagnose these patients earlier on. Furthermore, such facts may suggest that the actual frequency of immunological alterations is often underestimated. The general management of these patients should include specific clinical evaluation, with special attention to repeated ear, bronchial or digestive infections, lymphoproliferation, and symptoms of autoimmune diseases, mainly cytopenia, with appropriate immunological evaluation since diagnosis[4,7].

Finally, the importance of similar case reports to better understand the mechanisms involved in autoimmune phenomena correlated with KS is evident. The authors of this report understand that the absence of images of the patient may be a limiting factor for the analysis of the aforementioned case.

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