# Immune Manifestations in a Patient with Kabuki Syndrome: Case Report

## Kabuki Sendromlu Bir Hastada İmmünolojik Bulgular

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**ABSTRACT** Kabuki Syndrome (KS) is a very rare congenital disorder associated with multiple organ system involvement. Some recent studies suggest that KS is also associated with immune abnormalities and autoimmunity. However, the frequency and severity of the immune deficiency has not been clearly defined. We report a 6-year-old girl with the clinical features compatible with KS who suffered from recurrent infectious diseases such as meningitis, sepsis and skin abscesses. She had hepatosplenomegaly, thrombocytopenia, neutropenia, elevated serum IgM, IgA and IgG levels, positive direct Coombs test and mildly elevated double negative T cells (2.9%). The children with KS should be evaluated thoroughly at the time of diagnosis to reduce preventable morbidity and mortality.

**Key Words:** Congenital abnormalities; autoimmunity; apoptosis

**ÖZET** Kabuki sendromu (KS) çoklu organ tutulumu ile giden oldukça nadir bir doğmalık hastalıktır. Yakın zamandaki çalışmalarda KS'sinde immün bozukluklar ve otoimmünite varlığına işaret edilmiştir. Ancak, bu immün bozukluğun sıklığı ve şiddeti belirlenmemiştir. Burada klinik bulguları KS'yi düşündüren, menenjit, sepsis ve deri abseleri gibi tekrarlayan ciddi enfeksiyonları olan altı yaşındaki kız olgu takdim edildi. Fizik muayene ve laboratuvar bulguları ile; hepatosplenomegali, trombositopeni, nötropeni, artmış serum IgM, IgA ve IgG seviyeleri, direkt Coombs testi pozitifliği ve hafifçe artmış double negatif T (%2,9) hücrelerinin varlığı belirlendi. KS'li çocuklar erken dönemde morbidite ve mortalitenin önlenmesi amacıyla immünolojik yönden etraflıca değerlendirilmelidir.

**Anahtar Kelimeler:** Doğumsal anomaliler; otoimmünite; apoptoz

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The Kabuki syndrome (KS, OMIM 147920), also known as the Nikawa-Kuroki syndrome, is a multiple congenital anomaly/mental retardation syndrome characterized by a distinct facial appearance (reminiscent of the make-up of actors of Kabuki Japanese traditional theater).[1,2] KS has an estimated incidence of 1 in 32.000, and approximately 400 cases have been reported in Japan.[3] Courtens et al. reported further evidence that the KS is inherited as an autosomal dominant pattern.[4] Affected individuals exhibit characteristic and unusual facial features, postnatal growth deficiency, mental retardation, skeletal and dermatoglyphic abnormalities.[5,6] The facial phenotype is very specific and easily recognizable.[4]

The first reported non-Japanese Asian case that has premature telarche was also from Turkey.[7]

Recently, the results of the study of Ng et al. suggest that mutations in MLL2 are a major cause of KS.[3]

Although, susceptibility to infections is frequent in both non-Japanese (64%) and Japanese (60%) patients, immunological features have been reported only twice in pubmed.[5,8] Autoimmune disorders especially idiopathic thrombocytopenic purpura and rarely hemolytic anemia, thyroiditis and vitiligo may be associated with KS.[9-12] Here, we present a KS patient with some unusual features like hepatosplenomegaly, neutropenia and mildly elevated double positive T lymphocytes (DNT).

## CASE REPORT

A 6-years-old female was followed in our hospital because of recurrent severe infectious diseases such as meningitis, sepsis and skin abscess since she was 2-years old. Hepatosplenomegaly was determined with the liver palpable at about 5 cm and the spleen 4 cm below the costal margins. This finding persisted since she was 2 years old and sometimes she needed erythrocyte transfusions. Her parents were non-consanguineous and healthy. On physical examination, she had a typical face with prominent eyelashes, thinned eyebrows, long palpebral fissures and mild lip pits that crucial in the diagnosis of KS (Figure 1). Her height was 103 cm (25-50 percentiles) and weight 14 kg (3-10 percentiles). There were hypo-pigmented areas and scars on her arms likely chickenpox, legs and hips. In addition, she had simian lines and mild mental retardation.

Laboratory findings were presented in Table 1. Bone marrow examination and chest X-ray was normal. Immunological evaluation showed, increased serum immunoglobulin levels [IgG 2280 (304-1231 mg/dl), IgA 572 (17-69 mg/dl) and IgM 1070 (32-203 mg/dl)] except that IgE. Nitroblue tetrazolium test was positive. In terms of lymphocyte subgroups, CD3 80% (57-81), CD4 34% (26-48), CD8 48% (20-42), CD16+56 2% (8-28) (absolute count was normal), CD19 13% (10-27), CD45RA 55% (61-87), CD45RO 46% (22-53) were normal but slightly different according to reference ranges. Although she had vaccinated with BCG, she had no scar and ppd reaction. She had a positive direct Coombs test but thyroid antibodies were negative. Interestingly, DNT cells were mildly elevated (2.9%). Since, the patient died unexpectedly on the last hospitalization, further immunologic and genetic evaluation couldn't be performed. She probably died due to severe hemolysis and anemia (Hb 2 g/dl).

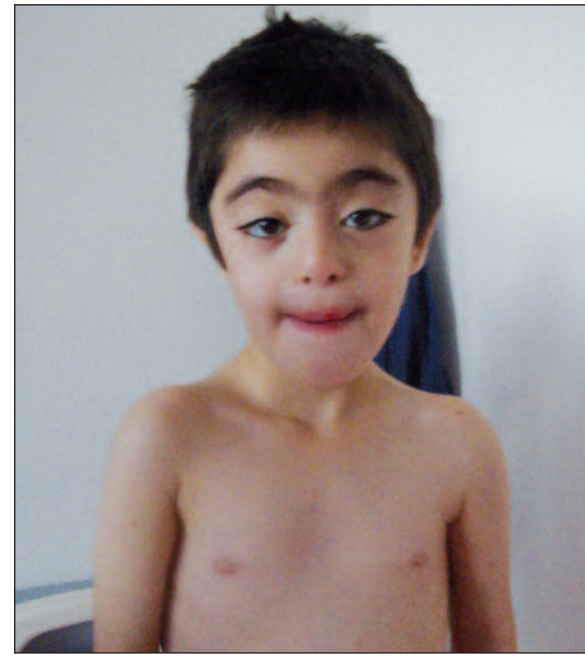

**FIGURE 1:** Facial appearance of the patient.
(See for colored form http://pediatri.turkiyeklinikleri.com/)

**TABLE 1:** Some blood parameters of the patient.

| | WBC (/µL) | Hb (mg/dL) | Lymphocyte (/µL) | Neutrophil (/µL) | Eosinophil (/µL) | Platelet (/µL) | D. Coombs |
|---|---|---|---|---|---|---|---|
| Feb 2006 | 10500 | 10 | 8100 | 1090 | 20 | 81400 | NA |
| Dec 2009 | 4300 | 9.6 | 3200 | 600 | 0 | 117000 | + |
| Jan 2010 | 2600 | 8.5 | 1900 | 100 | 100 | 9000 | + |

## DISCUSSION

In the largest review of KS, Wessels et al. reported frequent infections in 48% of three hundred patients.[13] Hoffman et al determined the serum immunoglobulin levels in 19 consecutive KS patients with or without frequent infections.[10] Sixteen (84%) of these 19 patients had some degree of hypogamaglobulinemia.[10] Chrzanowska et al.'s patients had also profound immunodeficiency with hypogamaglobulinemia and normal circulating B cells. These results suggest a presence of a functional defect in B cells or a T cell defect in these patients.[5,8,10] Shah et al. presented a KS patient had immunological findings consistent with common variable immunodeficiency. He also had alterations in his cardiac conduction system resulting some arryhtmias.[8]

Ming et al. evaluated autoimmune abnormalities in five KS patient. The patients had ITP (three patients), hemolytic anemia (two patients) and vitiligo (one patient).[9] Recently, MLL2 mutations have been shown to be a major cause of KS.[3]

Because of the presence of characteristic facies, susceptibility to infections and autoimmunity; the presented patient was diagnosed as KS, retrospectively. Immunological evaluation showed; elevated serum immunoglobulin levels, neutropenia (probably autoimmune), anemia, thrombocytopenia, positive Coombs test and mildly increased DNT cells. Neutropenia, hypergamaglobulinemia and elevated DNT have not been described previously in patients with KS. Although the molecular diagnosis could not be done, the presented case here seems to be a unique patient with KS.

Hepatosplenomegaly, autoimmune cytopenias, elevated serum immunoglobulin levels and mildly increased DNT count suggest autoimmune lymphoproliferative disease known as an apoptosis defect. In fact, there is a new genetic finding that MLL2 mutation in KS that could be related with apoptosis.[3] MLL2 (myeloid/lymphoid or mixed lineage leukemia 2) gene encodes a protein in SET family that is important in the epigenetic control of active chromatin state. In mice, this is related with apoptosis.[3] Because of the patient died, we could not perform genetic evaluation.

The patients with KS should be evaluated thoroughly to determine the range of immunological defects. This may help to discovering the functions of the responsible gene(s).

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