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ORIGINAL PAPER

Abdullah Alangari · Abdullah Abobaker · Hirokazu Kanegane · Toshio Miyawaki

X-linked lymphoproliferative disease associated with hypogammaglobulinemia and growth-hormone deficiency

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Abstract X-linked lymphoproliferative disease is a rare immunodeficiency disorder characterized by extreme vulnerability to Epstein-Barr virus, dysgammaglobulinemia, and very high incidence of lymphoma. Growth-hormone deficiency has been described in rare cases to be associated with certain immunodeficiencies, such as X-linked agammaglobulinemia. We report a first case with X-linked lymphoproliferative disease associated with hypogammaglobulinemia and growth-hormone deficiency, which was confirmed by *SAP* gene mutation. The patient's mutation is novel. He is also the first patient with X-linked lymphoproliferative disease to be reported from Saudi Arabia. The patient's Btk expression and *BTK* gene were normal. Patients with hypogammaglobulinemia and GH deficiency should be considered to have not only X-linked agammaglobulinemia, but also X-linked lymphoproliferative disease.

Keywords X-linked lymphoproliferative disease · Growth-hormone deficiency · Hypogammaglobulinemia · Lymphoma

Abbreviations XLP: X-linked lymphoproliferative disease · XLA: X-linked agammaglobulinemia · BTK: Bruton tyrosine kinase · GH: Growth hormone · SAP: SLAM (signaling lymphocyte activating molecule)-associated protein · EBV: Epstein-Barr virus

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A. Alangari (✉) · A. Abobaker
Department of Pediatrics, College of Medicine,
King Saud University,
P.O. Box 2925, 11461 Riyadh, Saudi Arabia
e-mail: alangari100@hotmail.com
Tel.: +966-14670807
Fax: +966-14679463

H. Kanegane · T. Miyawaki
Department of Pediatrics, Faculty of Medicine,
Toyama Medical and Pharmaceutical University,
Toyama, Japan

Introduction

X-linked lymphoproliferative disease (XLP, OMIM# 308240) is a rare inherited immunodeficiency characterized by extreme vulnerability to the Epstein-Barr virus (EBV). Patients present with fulminant infectious mononucleosis (60%), dysgammaglobulinemia (30%), and lymphoma (20–30%) [8]. Less commonly, they present with vasculitis or aplastic anemia. XLP is caused by mutation in the *SH2D1A* gene, which encodes a small cytoplasmic adapter protein known as SLAM-associated protein (SAP). XLP affects about 3 out of every 1,000,000 males, and is considered a fatal disease, with 70% of patients dying by the age of 10 years.

Growth-hormone (GH) deficiency has been reported in patients with hypogammaglobulinemia and an X-linked pattern of inheritance. The first report of such association was in 1980 by Fleihser et al. [5]. One member of that family was later shown to have normal *BTK* [11]. Some of the subsequently described patients, however, were determined to have X-linked agammaglobulinemia (XLA) with mutations in the *BTK* gene [3, 4]. To our knowledge, GH deficiency has never been reported in patients with XLP. Here, we report a 7-year-old Saudi boy who was diagnosed with XLP and growth-hormone deficiency.

Case report

A 7-year-old Saudi boy was admitted to our hospital because of recurrent infections and growth failure. At 7 months of age, he started to develop recurrent chest infections, otitis media and diarrhea. His birth weight was 2 kg and he continued to be small as compared to his peers. His parents were distant relatives. He had three sisters and four brothers who were all healthy. Physical examination showed that his

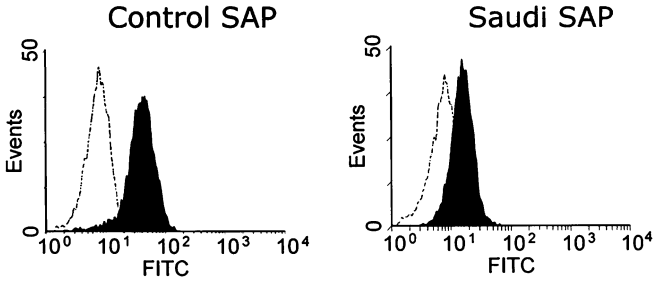

Fig. 1 Flow cytometry showing SAP expression in the patient's and a control's activated T-cells. Intracellular staining with FITC-labeled anti-SAP monoclonal antibodies was performed. SAP expression by activated T-cells from the patient was decreased compared to that from control. The *x-axis* indicates fluorescence intensity and the *y-axis* indicates relative cell number

height and weight were markedly below the fifth percentile for age. He had finger clubbing and small tonsils. A CBC showed WBCs of $28.4\times10^3\mu l^{-1}$, with absolute lymphocyte count of 20,000 μl^{-1}, and absolute neutrophil count of 6,000 μl^{-1}. His hemoglobin was 11.1 g/dl and platelets $299x10^3$ μl^{-1}. All immunoglobulin levels were extremely low: IgG<0.29 g/l (N. 6.3–12.8 g/l), IgM 0.13 g/l (N. 0.48–2.07 g/l), and IgA not detected (N. 0.33–2.02 g/l). Lymphocyte subset analysis (total lymphocyte count 20,000 μl^{-1}) showed 92% $CD3^+$ T (N. 55–78%), 25% $CD4^+$ T (N. 27–53%), 52% $CD8^+$ T (N. 14–34%), 4% $CD19^+$ B (N. 10–31%), and 1% $CD16/56^+$ NK cells (N. 6–27%). Delayed hypersensitivity skin testing for PPD and tetanus were negative. Bone age corresponded to 3–4 years. Thyroid hormones were normal. GH levels after insulin and clonidine stimulation were investigated and found to be significantly low with highest level being 5.6 ng/ml (peak GH level should be >10 ng/ml). GH concentrations during sleep were less than 2.5 ng/ml. These results indicated GH deficiency in this patient.

The patient was started on intravenous immunoglobulin replacement therapy. Because of the reports of XLA and GH deficiency, the *BTK* gene mutation was investigated, but the patient had no mutation. A few months later he developed a progressive left cervical lymph node enlargement. An open biopsy was consistent with diffuse large B-cell non-Hodgkin's lymphoma. The concurrence of hypogammaglobulinemia and lymphoma raised a possibility that he might have XLP. We found that SAP expression by activated T-cells from the patient was lower than in a control (Fig. 1) [10]. Mutation analysis of the *SH2D1A* gene showed a novel missense mutation (His8Pro) (Fig. 2). These results indicated that the patient had XLP. EBV serology was positive for EBV early antigen (21.56 AU/ml, positive >20) and EBV nuclear antigen (25.58 AU/ml, positive >20), suggesting a reactivation of EBV infection. According to the patient's history, there was no clinical evidence of EBV infection in the past.

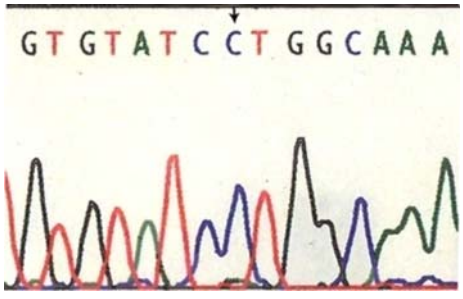

Fig. 2 Direct sequencing of the *SH2D1A* gene from the patient. A missense mutation of 322A>C (indicated by *arrow*) occurred in exon 1 of the *SH2D1A* gene, leading to a change in the amino acid sequence from histidine (CAT) to proline (CCT) in the eighth position of SAP

Discussion

Since the gene responsible for XLP was identified, this disease has been reported in many countries and in different ethnic backgrounds. Recently an Iranian XLP patient who presented initially with common variable immunodeficiency was described from the Middle East [1]. Our patient is the first to be reported from Saudi Arabia. He had large B-cell non-Hodgkin's lymphoma. Malignant lymphomas in XLP patients are largely of B-cell immunophenotype and are characterized by a small non-cleaved (Burkitt's, 53%), immunoblastic (18%), or non-cleaved large cell (12%) histology [8]. Occasionally, patients develop Hodgkin's disease or T-cell lymphoma. In this patient, the immunoglobulin levels were very low. The B-cell percentage was low (4%), but the absolute number was normal due to the high absolute lymphocyte count. This may be related to active EBV infection. In general, the role of EBV in the development of lymphoma or dysgammaglobulinemia remains unclear. Sumegi et al. [12] showed that at least 12.5% of patients with XLP could develop lymphoma or dysgammaglobulinemia with no evidence of EBV infection. The number of those patients was not significantly different from EBV+XLP patients.

Since the first report of hypogammaglobulinemia and GH deficiency in a family with an X-linked pattern of inheritance, a handful of patients with XLA and GH deficiency have been reported in the literature. Buzi et al. [2] investigated seven patients with XLA. Six of them had a growth pattern consistent with delay in puberty. Four of those six patients were young adolescents with GH deficiency. GH could be induced by testosterone in all of these patients except one. It was suggested that in some patients with XLA, delay in growth and puberty occurs, as has already been described for other chronic diseases. GH deficiency was reported in one patient with hyper-IgM syndrome [9] and in another patient with Shwachman-Diamond syndrome and hypogammaglobulinemia [7].

The association between growth retardation and immunodeficiency was recently reported in a patient who was found to have a mutation in the *STAT5b* gene [6]. However, this patient had high GH levels, most likely because STAT5b is downstream from the GH receptor. STAT5b is also critical in mediating the action of certain cytokines such as IL-2, 7, and 9, which may explain the recurrent and opportunistic infections in that patient.

Our patient underwent a bone-marrow transplant from an HLA-identical sister. Unfortunately, he died of post-transplant complications a few months later. We could not, therefore, reevaluate his GH production post-transplant. Although GH deficiency in our patient might be secondary to chronic illness, we believe that the growth pattern of patients with XLP should be evaluated carefully and GH production should be assessed for patients of short stature. This may help to elucidate the mechanism of GH deficiency in XLP and perhaps in some other immunodeficiencies. In conclusion, patients with hypogammaglobulinemia and GH deficiency should be considered to have not only X-linked agammaglobulinemia, but also X-linked lymphoproliferative disease.

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