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Case Report

Identification of an *SH2D1A* Mutation in a Hypogammaglobulinemic Male Patient with a Diagnosis of Common Variable Immunodeficiency

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Abstract

Common variable immunodeficiency (CVID) is a highly heterogeneous disease with an unpredictable pattern. CVID appears to have an immunologic and clinical phenotype similar to some hereditary humoral immunodeficiencies, including X-linked lymphoproliferative disease (XLP). The differential diagnosis of CVID and XLP is clinically of importance, because the two diseases have markedly different prognoses and treatment. The recent identification of the XLP gene, known as *SH2D1A*, has permitted a definitive diagnosis of XLP. In this report, we describe a male patient with XLP who initially received a diagnosis of CVID and developed a fatal course. Using genetic analysis, we confirmed that the patient harbored the *SH2D1A* gene mutation. The results support the notion that the possibility of a *SH2D1A* gene mutation should be considered in hypogammaglobulinemic male patients before a diagnosis of CVID is made. *Int J Hematol.* 2003;78:45-47.

Key words: Common variable immunodeficiency; X-linked lymphoproliferative disease; *SH2D1A*; Fatal complication

1. Introduction

Common variable immunodeficiency (CVID) is the most common humoral immunodeficiency among predominantly antibody deficiencies. It is characterized by variably decreased levels of all immunoglobulins in the serum, an abnormal specific antibody response, and variable numbers of T-cells and B-cells [1]. In addition to recurrent bacterial infections, patients with CVID have been observed to develop autoimmune phenomena and gastrointestinal diseases [1,2]. Despite many investigations for possible genetic and immunologic backgrounds in patients with CVID, no unifying defect has been identified [3-7]. The recent identification of genes responsible for hereditary humoral immunodeficiencies has shown that a proportion of patients with diagnoses of CVID suffer X-linked agammaglobulinemia (XLA) [8], X-linked and autosomal recessive hyper–immunoglobulin M (IgM) syndrome [9-11], or X-linked lymphoproliferative disease (XLP) [12,13]. Therefore, the current consensus is that a diagnosis of CVID should be given after molecular analysis results have excluded these hereditary humoral immunodeficiencies.

XLP is usually characterized by an extreme vulnerability to Epstein-Barr virus (EBV) infection, resulting in fatal infectious mononucleosis [14]. Other salient clinical features are non-Hodgkin's lymphoma and hypogammaglobulinemia [15,16]. The gene responsible for XLP has recently been identified and has been termed *SH2D1A/DHSP* or *SAP* (signaling lymphocytic activation molecule–associated protein) [17-19]. The employment of a mutational analysis for the XLP gene has permitted definitive diagnosis in presumed XLP patients, even without the family history. The differential diagnosis of CVID and XLP is clinically important and essential, because the two diseases have markedly different prognoses and treatments. In this report, we describe a male patient with XLP who initially received a diagnosis of CVID and developed a fatal course. Using genetic analysis, we identified the *SH2D1A* gene mutation in the patient.

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2. Patient, Materials, and Methods

2.1. Patient Report

The patient was an Iranian male, the first child of consanguineous parents with no family history suggestive of X-linked immunodeficiency disorders. He had been fully immunized without complications and was well until the age of 2 years, when he had *Haemophilus influenzae* meningitis. From the ages of 2 to 12 years, the patient had recurrent episodes of upper and lower respiratory infections requiring frequent oral antibiotics and hospitalization, and he also developed vitiligo. At the age of 12 years, the patient was referred to Children's Medical Center Hospital, Tehran, Iran, for evaluation. Immunologic investigation showed hypogammaglobulinemia (IgG, 300 mg/dL; IgA, 10 mg/dL; IgM, 30 mg/dL) with a normal number of circulating B-cells (10%). The diagnosis of CVID was made, and the patient was started on intravenous immunoglobulin (400 mg/kg every 3 weeks). At the age of 16 years, he began to suffer mild neutropenia, which progressed over a year to pancytopenia. At age 17, the patient was admitted to the hospital with severe pancytopenia. The bone marrow aspirate showed hypocellularity, and a diagnosis of aplastic anemia was made. The patient was treated initially with steroids for aplastic anemia; however, the treatment was not effective, and he died from overwhelming infection. Although we did not have EBV serologies, there was no clinical evidence of prior EBV infection. Because of the development of fatal complications, we considered the possibility of XLP in this case.

2.2. Mutation Analysis of the SH2D1A Gene

Genomic DNA was extracted from EBV-transformed B-lymphocytes, which had been established from the patient and the peripheral blood of other patients with CVID. Mutation analysis for the *SH2D1A* gene was performed by polymerase chain reaction (PCR) amplification of genomic DNA with *SH2D1A*-specific primers and single-strand conformation polymorphism (SSCP) analysis. PCR-SSCP analysis demonstrated that the patient had an abnormally mobilized exon 1 band compared with controls (Figure 1A), although he had similar patterns for other exons (data not shown). Sequencing reactions were performed with the BigDye terminator cycle-sequencing kit (Applied Biosystems, Foster city, CA, USA) with an automated ABI PRISM 310 Genetic Analyzer (Applied Biosystems). DNA sequencing results indicated the presence of a single point mutation (intron 1 +1, G→A) in a donor site for exon 1 of the *SH2D1A* gene (Figure 1B). Although complementary DNA from the patient was not available, such an alteration of an invariant splice donor site seemed to cause a truncated protein or a reduced messenger RNA, presumably resulting in the clinical manifestation as XLP.

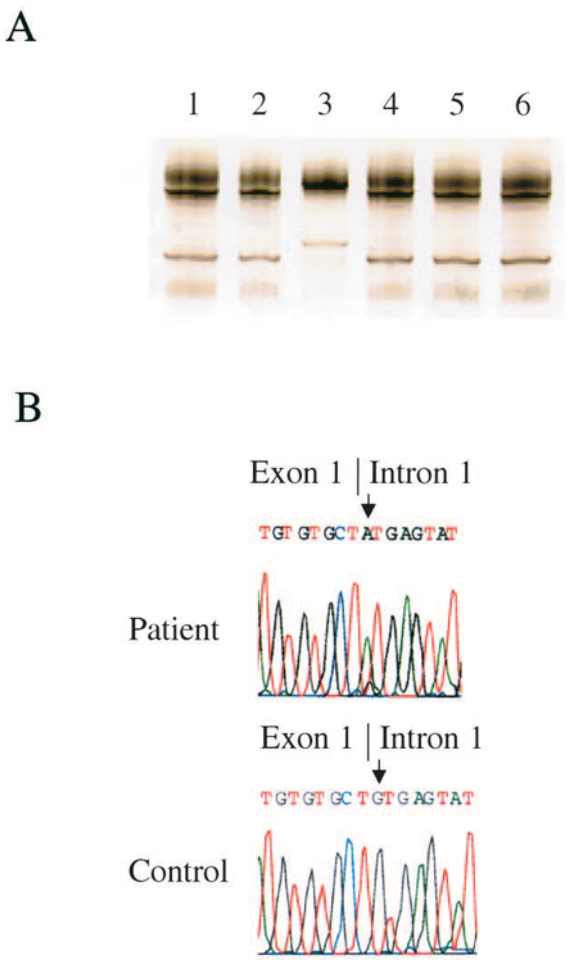

Figure 1. Mutation analysis of the *SH2D1A* gene. A, Polymerase chain reaction–single-strand conformation polymorphism analysis of exon 1 of the *SH2D1A* gene from the patient and healthy controls. Abnormal mobility was demonstrated in lane 3 (the patient). Other lanes indicate CVID patients as controls. B, Electropherograms of exon 1 of the *SH2D1A* gene from the patient and a healthy control. A substitution of G with A at an invariant +1 position of the splice donor site of exon 1 was shown in the patient. Arrowhead notes the mutation site.

3. Discussion

CVID is a heterogeneous syndrome with a wide variety of clinical manifestations and complications [1]. Although many studies have attempted to determine the genetic background in CVID, no underlying genetic defect has been identified. Generally, the diagnosis of CVID is based only on a clinical history of recurrent infections associated with hypogammaglobulinemia in the presence of a variable number of circulating B-cells. The important point is that the genetic exclusion of known hereditary humoral disorders, such as XLA, X-linked and autosomal recessive hyper-IgM syndrome, or XLP, is necessary before a diagnosis of CVID is employed. Usually, typical XLP can be diagnosed on the basis of some clinical criteria. Yin et al [20] showed in an *SH2D1A* gene mutation study that a history of hypogammaglobulinemia after EBV infection was an appropriate inclusion criterion. In addition, mutations in the *SH2D1A* gene were found in 34 patients (97%) in an analysis of 35 male patients with XLP phenotypes [21]. The results of these studies suggest that the occurrence of hypogammaglobulinemia after EBV infection

and an X-linked pedigree of immunodeficiencies can be considered to indicate the existence of XLP.

The patient described here presented with symptoms in early childhood. Based on the decreased levels of all immunoglobulins, the normal number of circulating B-cells, as well as the absence of an X-linked pedigree of immunodeficiencies, a diagnosis of CVID was initially made for the patient. In cases in which a single male patient manifests the typical XLP phenotype and in atypical cases without a history of EBV infections, a diagnosis for XLP is more difficult [22]. There is evidence that some patients with a diagnosis of CVID appear to have mutations in the *SH2D1A* gene [12,13]. Although EBV infection is known to be the major trigger for the XLP phenotypes [14,23], it has been reported that at least 10% of XLP cases are driven without an EBV infection [21]. Our patient developed severe pancytopenia at the age of 17 years and unfortunately died of overwhelming infection.

The prognosis for XLP is in general much worse than for CVID. Survival beyond the second decade of life is unusual, and no XLP patients older than 40 years have been described [24]. At present, the only definitive treatment that may cure XLP and prevent complications is allogeneic bone marrow transplantation [16,25,26]. Early definitive diagnosis of XLP in affected male patients should allow the introduction of early treatment, including immunoglobulin prophylaxis and more aggressive therapy, such as bone marrow transplantation, as well as better genetic counseling.

In conclusion, we have demonstrated the presence of *SH2D1A* mutations in a male patient who originally received a diagnosis of CVID and developed a fatal course. We propose that the possibility of *SH2D1A* gene mutation should be considered in hypogammaglobulinemic male patients before a diagnosis of CVID is given.

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