Hyper IgM Syndrome Type 2 Presenting as Intestinal Lymphoid Polyposis Without Recurrent Infection

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Hyper IgM syndrome (HIGMS) comprises a group of primary immunodeficiencies [1] characterized by impaired immunoglobulin class-switch recombination (CSR). Patients with HIGMS have normal or elevated IgM levels, with the other immunoglobulin subtypes absent or strongly decreased. In some HIGMS types, impaired somatic hypermutation (SHM) of immunoglobulin genes and abnormal T-cell function are also present [2].

HIGMS type 1 (HIGMS1) is caused by mutations in the gene encoding CD40 ligand (*CD40L*), and HIGMS3 is due to mutations in the *CD40* gene. HIGMS1 and HIGMS3 are clinically indistinguishable. HIGMS2 is produced by mutations in the activation-induced cytidine deaminase gene (*AICDA*) [3], and HIGMS5 is caused by mutations in the uracil-DNA glycosylase gene (*UNG*). These types are clinically similar. Most patients with HIGMS develop clinical symptoms in infancy and early childhood. All the forms of HIGMS are characterized by increased susceptibility to recurrent bacterial infections of the respiratory and digestive tracts [4,5]. Viral infections are more frequent and severe. Patients with defects in the CD40/CD40L pair also have defective cellular immunity and are susceptible to opportunistic infections such as *Pneumocystis jiroveci* pneumonia. Since cellular immunity is not impaired in HIGMS owing to mutations in *AICDA* or UNG, patients with HIGMS2 and HIGMS5 do not experience opportunistic infections. In these types, lymphadenopathy due to the presence of expanded germinal centers is frequent, whereas the lymph nodes of patients with mutations in *CD40L* and *CD40* lack germinal centers.

Activation-induced cytidine deaminase (AID) is expressed in B cells in germinal centers, where it plays a key role in both CSR and SHM. Patients with HIGMS2 first experience recurrent infections during early childhood. However,

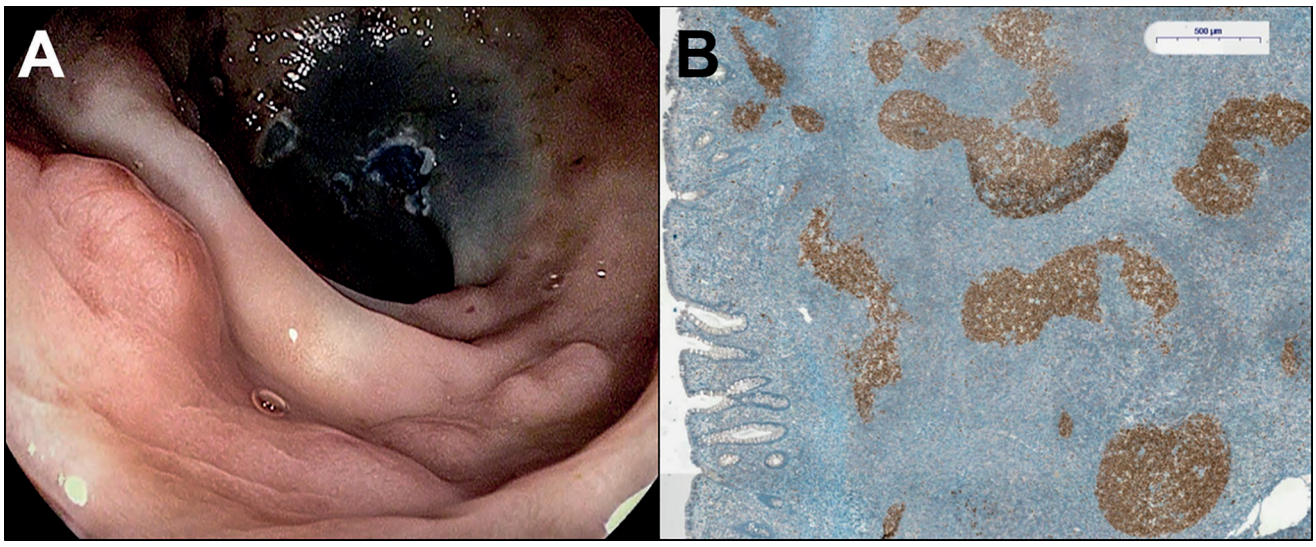

Figure. A, Colonoscopy image showing several subcentimeter sessile polyps with a lymphomatous appearance in the sigmoid colon. B, Immunohistochemistry study of a lymphoid colon polyp with large germinal centers and BCL6 expression.

because of the absence of opportunistic infections, many patients are diagnosed in the second or third decade of life. Lymphadenopathy is a clinical manifestation caused by the enlargement of germinal centers. Lymphoid hyperplasia predominantly affects the tonsils and cervical lymph nodes [6].

We report the case of a patient with HIGMS2 confirmed by the finding of 2 mutations in *AICDA* that presented as intestinal lymphoid polyposis and without recurrent bacterial infections.

A 26-year-old Chinese man with vertically acquired chronic hepatitis B was admitted to the Digestive Department with rectal bleeding. On admission, he did not have an active bacterial infection and did not report a prior history of recurrent infections.

During hospitalization, the patient underwent lower gastrointestinal endoscopy, which revealed multiple polyps measuring between 5 mm and 15 mm in diameter and distributed throughout the sigmoid colon, rectum (Figure, A), and terminal ileum (Supplementary Figure 1A). Upper gastrointestinal endoscopy findings were normal. A computed tomography scan showed asymmetric polypoid thickening of the rectum wall, with several considerably enlarged locoregional lymph nodes (Supplementary Figure 1B). Histopathology of the polyps revealed hyperplastic lymphoid tissue with large and irregular germinal centers and no morphological or immunohistochemical signs of malignancy (Figure, B). Flow cytometry analysis of the lymphocytes extracted from biopsied tissue revealed a B-cell population of 62% ($CD19^+$) and a T-cell population of 38% ($CD3^+$), neither of which was characterized by phenotypic aberrations. Analysis of *IGH* gene rearrangements by polymerase chain reaction assay did not reveal B-cell clonality. Therefore, the patient was diagnosed with intestinal benign lymphoid polyposis.

Serum IgM was elevated (2514 mg/dL), and IgG, IgA, and IgE were undetectable. The patient was referred to the Immunology Department for investigation of immunodeficiency. HIGMS2 was suspected, and Sanger sequencing of the *AICDA* gene disclosed 2 heterozygous mutations, namely, c.295C>T (p.Arg99*) (Supplementary Figure 1C) and c.520A>G (p.Arg174Gly) (Supplementary Figure 1D). These results confirmed the diagnosis of HIGMS2.

Benign lymphoid polyposis (BLP) of the gastrointestinal tract is a relatively frequent process in childhood, although very infrequent in adults. It is characterized by the presence of lymphoid polyps in the colon and, occasionally, in the terminal small intestine. The pathogenesis of BLP in adults is largely unknown, although, in some cases, it has been associated with immunodeficiency states such as common variable immunodeficiency, hypogammaglobulinemia, selective IgA deficiency, and HIV infection [7]. Massive intestinal lymphoproliferation has been documented in a patient with HIGMS [8]; however, the present case is the first with HIGMS2 confirmed in a patient with BLP of the gastrointestinal tract. Interestingly, in *AID*-deficient knockout mice, the development of a striking number of protruding follicular structures has been reported in the small intestine [9]. These structures are derived from Peyer patches and from isolated lymphoid follicles present in the lamina propria and are filled with IgM-bearing B cells.

The finding of 2 mutations in the *AICDA* gene confirmed the diagnosis of HIGMS2, although neither mutation has been previously described. The c.295C>T mutation introduces a premature termination codon, p.Arg99*, which generates a truncated protein. The second mutation, c.520A>G, causes a nonconservative amino acid substitution, p.Arg174Gly. The affected amino acid residue is highly conserved in terms of evolutionary changes, and bioinformatics analysis using PolyPhen2 predicts that p.Arg174Gly is a pathogenic variant with the highest score.

A striking characteristic of the present case is that the patient did not present with a bacterial infection and did not report a history of recurrent infections in childhood or more recently, possibly because of the nature of the missense

mutation p.Arg174Gly. While CSR and SHM are both dependent on *AID*, they are independent events. The activity responsible for SHM resides in the C-terminal domain of *AID*, in addition, this domain interacts with a cofactor necessary for this activity. Some mutations located in the C-terminal domain of *AID* result in defective CSR, whereas SHM is not affected. This hypothesis should be investigated, although it is possible that the p.Arg174Gly mutant *AID* retains SHM activity, as arginine 174 is located in the C-terminal domain. In this case, IgM antibodies harboring somatic mutations could be produced, and it has been demonstrated that these antibodies can protect against infection [10]. Therefore, it is possible that the high levels of IgM antibodies in the patient's serum could have prevented recurrent bacterial infections. The patient initiated treatment with intravenous immunoglobulin, which had to be withdrawn because of adverse effects. Nonetheless, he remains free of recurrent infections. Other cases of HIGMS2 without recurrent infection have been reported [11].

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentations

This case was presented in poster format at "I congreso interdisciplinar en genética humana" in 2017.

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