Hyper IgM syndrome type 2 presenting as intestinal lymphoid polyposis and without recurrent infections

Running title: Hyper IgM syndrome and intestinal polyps

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**Palabras clave:** Síndrome de hiper-immunoglobulina M, La Deaminasa de Citosina Inducida por Activación (AICDA), Poliposis linfomatosa benigna, Infecciones bacterianas.

Hyper-immunoglobulin M syndromes (HIGMS) are a group of primary immunodeficiencies [1]. They are 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, an 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. In all forms of HIGMS, there is an increased susceptibility to recurrent bacterial infections of the respiratory and digestive tracts [4,5]. Viral infections are also 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. Cellular immunity is not impaired in HIGMS due to
mutations in AICDA or UNG, and consequently, opportunistic infections are absent in HIGMS2 and HIGMS5 patients. In these types, lymphadenopathy due to the presence of expanded germinal centers is frequent, whereas lymph nodes of patients with mutations in CD40L and CD40 lack germinal centers.

Activation-induced cytidine deaminase (AID) is specifically intracellularly expressed in B cells in germinal centers, where it plays a key role in both CSR and SHM. Patients with HIGMS2 present with the onset of recurrent infections during early childhood. However, because of the lack of opportunistic infections, many patients are diagnosed in the second or third decade of life. Lymphadenopathy is a clinical feature, due to the enlargement of germinal centers. Lymphoid hyperplasia predominantly affects tonsils and cervical lymph nodes [6].

We report the case of a man with HIGMS2, confirmed by the finding of two mutations in AICDA, presenting as intestinal lymphoid polyposis and without recurrent bacterial infections.

A 26-year-old male from China was admitted to the Digestive Department with rectal bleeding. The patient had active chronic hepatitis B, acquired through vertical transmission. On admission, he did not show an active bacterial infection and did not report a prior history of recurrent infections.

During hospitalization, the patient was subjected a lower gastrointestinal endoscopy revealing multiple polyps, between 5 and 15 mm in diameter, distributed throughout the sigmoid colon, rectum (Figure 1A) and terminal ileum (Supplementary Figure 1A). An upper gastrointestinal endoscopy was normal. A computed tomography scan showed an asymmetric polypoid thickening of the rectum wall, with several
locoregional adenopathies of a significant size (Supplementary Figure 1B). Histopathological examination of the polyps revealed hyperplastic lymphoid tissue with large and irregular germinal centers, without morphological or immunohistochemical signs of a malignancy (Figure 1B).

Flow cytometry analysis of the lymphocytes extracted from biopsied tissue showed 62% of B cells (CD19+) and 38% of T cells (CD3+), both without phenotypic aberrations. Analysis of IGH gene rearrangements by polymerase chain reaction did not detect B-cell clonality. Therefore, intestinal benign lymphoid polyposis was diagnosed.

In the serum, IgM was elevated (2,514 mg/dL), and IgG, IgA and IgE were undetectable. To investigate immunodeficiency, the patient was referred to the Immunology Department. HIGMS2 was suspected, and Sanger sequencing of the AICDA gene detected two mutations in heterozygosis, c.295C>T (p.Arg99*) (Supplementary Figure 1C) and c.520A>G (p.Arg174Gly) (Supplementary Figure 1D). These results confirmed the diagnosis of HIGMS2 in the patient.

Benign lymphoid polyposis (BLP) of the gastrointestinal tract is a relatively frequent process in the childhood but is very infrequent in adults. BLP 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, but 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 one 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 documented in the small intestine [9].

These structures are derived from Peyer's patches and from isolated lymphoid follicles present in the lamina propria and are filled with IgM-bearing B cells. The finding of two 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*, producing a truncated protein. The second mutation, c.520A>G, causes a nonconservative amino acid change, p.Arg174Gly. The affected amino acid residue is evolutionarily highly conserved, and bioinformatics analysis with 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 the childhood or more recently. The nature of the missense mutation p.Arg174Gly could explain this fact. Although 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, or perhaps, this domain interacts with a cofactor necessary for this activity. It is known that some mutations located in the C-terminal domain of AID result in defective CSR, whereas SHM is not affected. This hypothesis should be investigated, but it is possible that the p.Arg174Gly mutant AID retains the 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 infections [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, but it had to be withdrawn because of adverse effects. Nonetheless, he continues without recurrent infections. Other HIGMS2 patients without recurrent infections have been described.

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CONFLICTS OF INTEREST
The authors declare that they have no conflicts of interest.
References


**Figure 1.** A) Colonoscopy image showing several subcentimeter sessile polyps of the lymphomatous appearance in the sigmoid colon. B) Immunohistochemical study of a lymphoid colon polyp with large germinal centers and BCL6 expression.