ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Atypical presentation of X-linked hyper-IgM syndrome simulating inflammatory bowel disease

Apresentação atípica de síndrome de hiper-IgM ligada ao X simulando doença inflamatória intestinal

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ABSTRACT

We report the case of a male patient, who started with ulcers in the gastrointestinal tract, associated with recurrent fever and diarrhea with mucus and blood at 10 months of life, initially suspected of inflammatory bowel disease, however, he did not improve the condition with immunosuppressive therapy, being investigated for inborn error of immunity. In laboratory tests, he had low levels of IgG and IgA and high levels of IgM and persistent neutropenia. Therefore, a genetic test was performed and confirmed the diagnosis of X-linked hyper IgM syndrome. Inborn errors of immunity can manifest relatively frequently with diseases of the gastrointestinal tract, and should be included as a differential diagnosis of chronic diarrhea. Included in this group of diseases, hyper-IgM syndromes constitute a heterogeneous group of diseases, having in common significantly low or absent levels of IgG and IgA and normal or high levels of IgM, which predispose to infections and recurrent fever; in addition to other laboratory alterations, such as neutropenia, which may be associated with ulcers in the gastrointestinal tract and proctitis, simulating the clinical presentation of inflammatory bowel disease. For the reported patient, therapy with immunoglobulins was started periodically, in addition to antibiotic prophylaxis for infections, evolving with a satisfactory clinical response. The main objective of the article is to alert to the differential diagnosis of inborn errors of immunity in view of the presented condition, aiming at early diagnosis and the institution of adequate therapy.

Keywords: Primary immunodeficiency diseases, immune system diseases, hyper-IgM immunodeficiency syndrome type 1.

RESUMO

Relatamos o caso de um paciente do sexo masculino, que iniciou quadro de úlceras em trato gastrointestinal, associado a febre recorrente e diarreia com muco e sangue aos 10 meses de vida, suspeitado inicialmente de doença inflamatória intestinal, no entanto, não apresentou melhora do quadro com terapia imunossupressora, sendo realizada investigação para erro inato da imunidade. Nos exames laboratoriais, apresentou níveis baixos de IgG e IgA e níveis elevados de IgM e neutropenia persistente. Diante disso, foi realizado teste genético que confirmou diagnóstico de síndrome de hiper-IgM ligada ao X. Os erros inatos da imunidade podem se manifestar com doenças do trato gastrointestinal, de forma relativamente frequente, devendo entrar como diagnóstico diferencial de diarreia crônica. Inclusa nesse grupo de doenças, as síndromes de hiper-IgM constituem um grupo heterogêneo de doenças, possuindo em comum níveis significativamente baixos ou ausentes de IgG e IgA e níveis normais ou elevados de IgM, o que predispõe a infecções e febre recorrente; além de outras alterações laboratoriais, como neutropenia, que pode estar associada a úlceras no trato gastrointestinal e proctite, simulando apresentação clínica de doença inflamatória intestinal. Para o paciente relatado, foi iniciada terapia com imunoglobulinas de forma periódica, além de antibioticoprofilaxia para infecções, evoluindo com resposta clínica satisfatória. O artigo possui objetivo principal de alertar para o diagnóstico diferencial de erros inatos da imunidade diante do quadro apresentado, visando o diagnóstico precoce e a instituição da terapia adequada.

Descritores: Doenças da imunodeficiência primária, doenças do sistema imunitário, síndrome de imunodeficiência com hiper-IgM tipo 1.

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Submitted: 07/06/2021, accepted: 10/12/2021.

Arq Asma Alerg Imunol. 2021;5(4):426-32.

http://dx.doi.org/10.5935/2526-5393.20210063

Introduction

Inborn errors of immunity (EII) are genetic disorders that affect different components of the immune system. Currently, due to the improvement of genetic diagnosis methods, more than 400 diseases are described. However, late or incorrect diagnosis is still common.[1,2] Clinical manifestations are very diverse, being characterized by severe recurrent or prolonged infections, autoimmune/inflammatory disease, allergy or malignancy.[3,4]

EII can affect the gastrointestinal tract at a frequency ranging from 5% to 50%.[1] The intestine-associated lymphoid tissue is the largest lymphoid organ in the body, with varied mechanisms of immune regulation. Diarrhea and malabsorption are common in many EII. Recurrent or treatment-refractory gastrointestinal diseases should be a warning sign for a possible immunodeficiency.[5]

Hyper-IgM syndrome (HIGM) can be congenital or secondary to other underlying diseases (multiple myeloma, leukemia, nephrotic syndrome, and chronic infections, such as congenital rubella syndrome and use of medications such as phenytoin).[6] Congenital forms are very rare, accounting for 0.3 to 2.9% of all primary immunodeficiencies, with an estimated incidence of 1/130,000 live births and with heterogeneous genetic defects, which may present X-linked, autosomal recessive inheritance or dominant.[3,7,8] In HIGM, there is a defect in immunoglobulin class switching due to genetic defects in the CD40 (B lymphocyte)/CD40 binding (CD40L; T lymphocyte) signaling pathway or in the DNA repair system responsible for class switching. Therefore, there is a loss in the signaling necessary for activated T lymphocytes to induce B lymphocytes to convert immunoglobulin M (IgM) into other immunoglobulins (IgG, IgA and IgE).[2,9,10] In addition, CD40L also participates in the maturation of antigen-presenting cells, in stimulating the effective function of macrophages and in the enhancement of T lymphocyte antigens.[8,11,12]

Depending on the associated genetic defect, HIGM can be classified into five subtypes: type 1, occurs due to CD40L deficiency, is X-linked autosomal dominant hereditary, exclusive to males and the most common form, corresponding to 65% of cases;[5] type 2, corresponds to the autosomal recessive form with mutations in the gene that encodes a cytidine deaminase that participates in the intracellular activation cascade of the B lymphocyte.[5] These patients may have adenoid hyperplasia with defects in the germinal centers, representing about 15% of cases; type 3, the mutation occurs in the gene that specifically codes for the CD40 molecule essential in lymphocyte development, growth, and differentiation; type 4, whose molecular mechanisms are still unknown; and type 5, produced by mutations in the gene for a glycosylase (uracil DNA glycosylase), the last two being recessive forms.[6] All these syndromes have similar clinical characteristics and only through molecular and genetic studies is it possible to make a differential diagnosis.[1,13] The patients have as characteristics significantly low or absent levels of IgG and IgA and normal or high levels of IgM, in addition to a weak or non-protective IgG response to vaccinations.[14] Neutropenia is the most common hematological alteration in type 1 HIGM, but its cause remains unknown, and it may be due to the presence of antineutrophil antibodies and/or delay in myeloid maturation in the marrow.[15] Some studies suggest that CD40-ligand may also act to stimulate the endogenous production of granulocyte colony stimulator,[15] and bone marrow biopsies from these patients may show delay in myeloid lineage maturation.[14]

Most patients with HIGM have increased susceptibility to infections, especially sinopulmonary, such as pneumonia, sinusitis and acute otitis media, developing symptoms during the first year of life; and almost all during the first four years.[16] Pneumocystis is the most prevalent infection and in half of the cases it is caused by *Pneumocystis jirovecii*.[16] Infectious complications of the respiratory tract, such as bronchiectasis, are common.[9] Infectious diarrhea has been associated with infection by cryptosporidium, giardia, salmonella or entamoeba.[2] Aphthous ulcers, gingivitis and rectal ulcers may be associated with chronic or intermittent neutropenia.[2] Central nervous system infection, sepsis, hepatitis and/or sclerosing cholangitis, cellulitis and/or subcutaneous abscesses may also occur.[16] Due to recurrent infections, these patients may have growth and development failure.[16,17] There is an increased risk of neoplasms, especially of the liver and biliary tract, and of autoimmune complications, such as sclerosing cholangitis, which may be associated with chronic infection by *Cryptosporidium parvum*.[9,16,18]

We report the case of a male patient who presented warning signs of innate immunity error, with severe infection, in addition to recurrent fever, chronic diarrhea, oral ulcers and neutropenia, initially being managed as an inflammatory bowel disease, however,

with confirmed later diagnosis of type 1 HIGM, with the aim of reminding us of this diagnostic hypothesis in the face of similar conditions.

Case report

Male patient, born by cesarean section, at term, non-consanguineous parents, one healthy sister, uneventful in the perinatal period, mixed breastfeeding from birth and introduction of food at 6 months, with normal growth and development. First admission at 6 months of age due to severe pneumonia, evolving with hyposaturation and severe respiratory distress, requiring admission to the intensive care unit, with orotracheal intubation and good response to broad-spectrum antibiotic therapy (piperacillin-tazobactam and vancomycin). He remained asymptomatic for up to 10 months of life, when he started a condition of ulcers in the oral cavity associated with daily fever, especially at night, seeking medical care sometimes, with antibiotic therapy with amoxicillin and amoxicillin-clavulanate, and the condition was reported according to the mother. with antibiotic therapy, however, return soon after the end of the medication. During this period, he even presented a condition described as dental abscess, as a complication of ulcers, which improved after the use of antibiotics. At 12 months of age, he started with episodes of diarrhea with blood and mucus, 3-4 times a day and reddish plaques evolving to more intense hyperchromic spots on the lower limbs and knees, and was interrogated arthralgia (difficulty in resting feet on the floor). He was treated with antibiotics and steroids, with a good response.

He was hospitalized twice due to oral ulcers, fever and bloody diarrhea, being treated with antibiotic therapy. He was submitted to a cow's milk protein exclusion diet, however, he did not show improvement, and after reintroduction of this protein, there were no changes in the intestinal condition.

Thus, the gastroenterology service raised the hypothesis of inflammatory bowel disease, and upper digestive endoscopy was performed, which showed shallow esophageal ulcer, without significant microscopic changes, and colonoscopy that showed isolated, shallow ulcers, with adjacent enanthematic and edematous mucosa in the transverse colon, left colon, sigmoid and rectum, without inflammatory activity on microscopy. Therapy for inflammatory bowel disease was started with prednisone, azathioprine, sulfasalazine and adequate enteral formula. However, he persisted with fever of an intermittent pattern, oral and perianal ulcers, and diarrhea with blood and mucus, requiring hospitalization during the period for intravenous antibiotic therapy, with improvement in the condition. At 15 months of age, he was hospitalized for colitis-like diarrhea, suspected of EII and an evaluation was requested from the Immunology service, with the initial hypothesis being a deficiency of IL10/IL10 receptor and a genetic panel for EII was requested. At the same time, other immunoglobulin tests and immunoglobulin dosage were requested, showing IgG and IgA below the 3rd percentile and IgM above the 97th percentile. The immunoglobulin dosage was repeated, keeping IgA and IgG below the 3rd percentile (P3) for age and normal IgM, intravenous immunoglobulin replacement was started, steroids and immunosuppressants were suspended, and antimicrobial therapy was maintained, with clinical and laboratory improvement. The review of blood counts showed intermittent anemia and persistent neutropenia since 12 months of life. Myelogram with bone biopsy was also performed, showing erythroid and granulocytic hypocellularity with moderate delay in myeloid maturation. The patient received granulocyte colony stimulator therapy, with significant improvement in neutropenia. Vitamin B 12 and folic acid levels were normal and other tests had already been performed, such as serology for Epstein-barr virus and cytomegalovirus with negative IgG and IgM, negative anti-HIV, in addition to pANCA and cANCA, fecal calprotectin, anti- fecal trypsin, HLAB51 negative. During hospitalizations, *Campylobacter jejunii* was isolated by multiplex PCR from feces, *Klebsiella* and *Citrobacter freundii* in urine cultures.

At 19 months of age, the result of the genetic panel for EII (407 genes investigated - Invitae laboratory) indicated a mutation in the CD40 ligand (Figure 1). Subsequently, flow cytometry was performed, which showed an alteration in the expression of the CD40L protein (Figure 2), and the amplification of the PCR product on an agarose gel showed absence of amplification of exons 4 and 5 (Figure 3), confirming the diagnosis of X-linked HIGM. No pathogenic mutations were observed in the other genes.

Discussion

X-linked HIGM or type 1 is characterized by CD40L deficiency, which affects males, in general, children of mothers who carry the mutation in one

RESULT: POSITIVE

One Likely Pathogenic variant identified in CD40LG. CD40LG is associated with X-linked hyper-IgM syndrome.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
CD40LG	Deletion (Exons 4-5)	hemizygous	Likely Pathogenic
IL17RA	c.355C>A (p.Leu119Met)	heterozygous	Uncertain Significance
PIK3R1	c.*1del (Non-coding)	heterozygous	Uncertain Significance
VPS13B	c.4329T>G (p.His1443Gln)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 207 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Figure 1
Genetic panel for Inborn Errors of Immunity (EII - 407 genes).

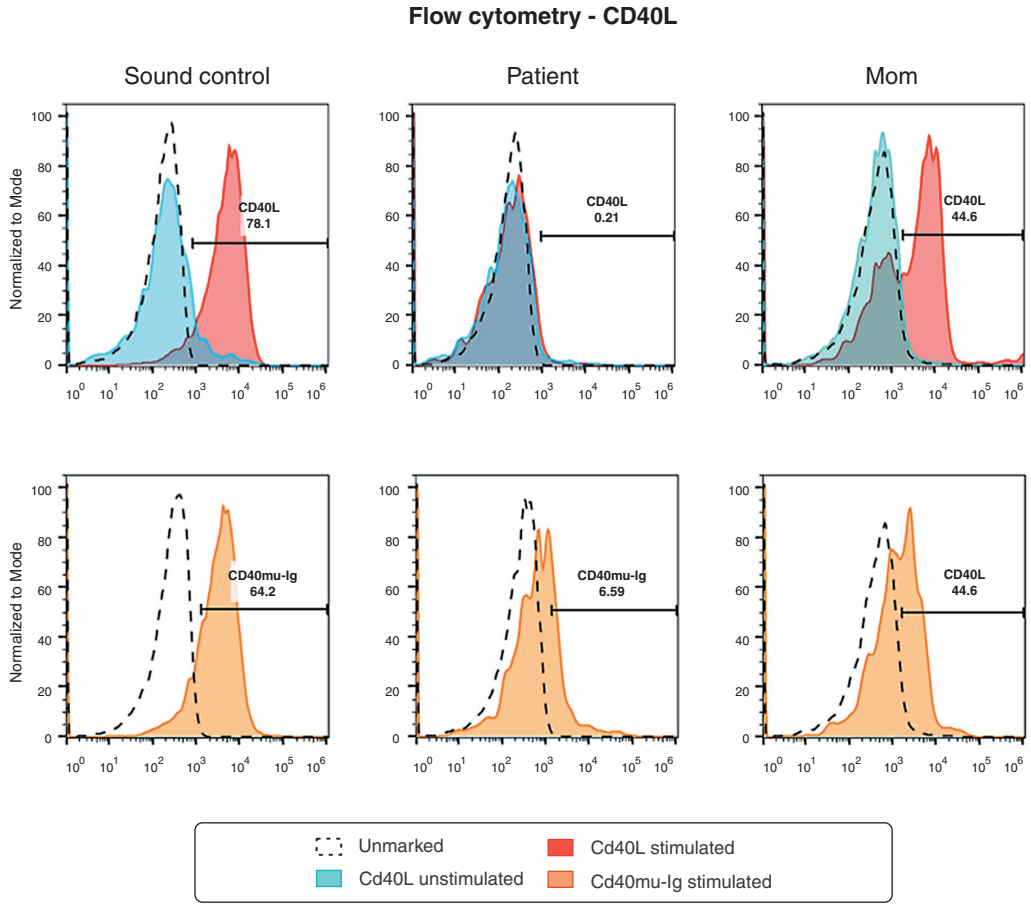

Figure 2
CD40 Ligand Protein expression by flow cytometry.

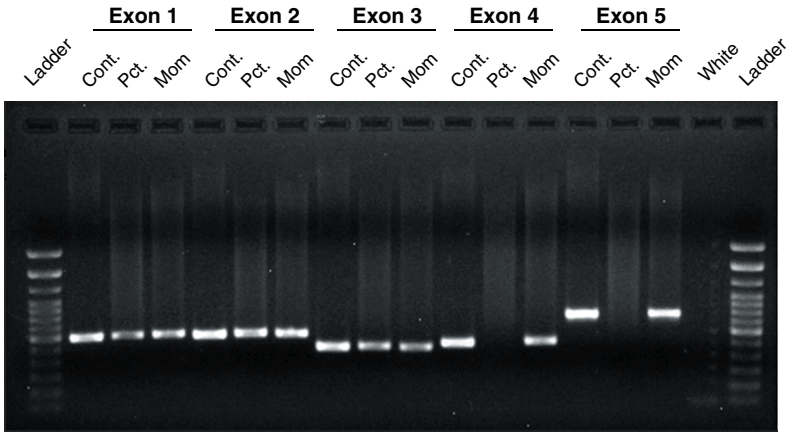

Figure 3
Amplification of CD40LG exons on agarose gel.

of the X chromosomes.[19] These patients have a defect in the function of B cells and T cells, which is considered a primary combined immunodeficiency.[20] The patient in the case reported is male and presented signs of primary immunodeficiency during the first year of life, due to severe pneumonia, requiring orotracheal intubation. Sinopulmonary infections, especially pneumonia, are present in 80% of patients with X-linked HIGM, occurring during the first year of life.[16] Approximately half of patients with HIGM have pneumonia caused by *P. jirovecii*.[16] As it is a combined immunodeficiency, these patients, in addition to being susceptible to infections by opportunistic bacteria, such as *P. jirovecii* and histoplasmosis, are also more prone to infections by encapsulated bacteria, such as Streptococcus pneumoniae or *Haemophilus influenzae*, which are likely to cause pneumonia presented by the patient. besides presenting a picture of recurrent fever with improvement after the use of antibiotic therapy and multiplex PCR of feces isolating bacteria, confirming the greater predisposition to infections.[16,17]

The patient also had chronic diarrhea, being a common manifestation of the X-linked Hyper-IgM syndrome and more commonly resulting from cryptosporidium infections.[16] Diarrhea associated with ulcers of the gastrointestinal tract could also be justified by persistent neutropenia, considered a common hematological finding present in this syndrome, present in two-thirds to half of patients, and may be episodic or recurrent, being associated with ulcers in the gastrointestinal tract, stomatitis and proctitis, in addition to increasing the risk of infections.[12,14,16] Bone marrow biopsy in these patients may show a delay in the maturation of the myeloid lineage, as in the case reported.[14]

Initially, inflammatory disease was suspected.early-onset intestinal ia; however, the patient did not have inflammatory markers compatible with inflammatory diarrhea, such as calprotectin and fecal alpha-1-antitrypsin, in addition to not presenting suggestive microscopy in ulcer biopsies and not showing a good response with the use of immunosuppressants. Furthermore, laboratory tests showed normal to high levels of IgM and low levels of IgE, IgG and IgA, in addition to neutropenia. Therefore, primary immunodeficiency was suspected, and the diagnosis of X-linked HIGM was confirmed through genetic testing.

The therapeutic options used include intravenous immunoglobulin replacement, antibiotic prophylaxis for *P. jirovecii* infection with sulfamethoxazole-trimethoprim, use of granulocyte colony stimulator for neutropenia and bone marrow transplantation, with

varying degrees of success[3,4,15,16,20]. In addition, it is not recommended that these patients receive live virus vaccines, and prevention of cryptosporidium infection (water contamination) should be recommended, with hygienic measures such as drinking only filtered water, not having contact with faeces and avoiding bathing in lakes, ponds, and in non-chlorinated pools.[7,12,14] The only curative therapy is allogeneic hematopoietic cell transplantation, with better results in young patients, without liver disease at the time of transplantation, and with good spinal cord suppression, which should be a considered therapeutic option.[9,14] In the case of the reported patient, clinical and laboratory improvement was observed with regular use of intravenous immunoglobulin IgG, in addition to good control of diarrhea, ulcers in the gastrointestinal tract and neutropenia with the use of granulocyte colony stimulator and prophylactic trimethoprim sulfamethoxazole; hygienic measures were also oriented to the mother.

Conclusion

X-linked HIGM should be remembered when there is increased susceptibility to infections, which may manifest as recurrent fever, chronic diarrhea and/or multiple hospitalizations for infectious conditions, associated with a reduction in IgG, IgA and IgE immunoglobulins, with IgM immunoglobulin normal or increased and neutropenia, especially in male patients. The main cause of death for these patients is opportunistic infections, hence the importance of early diagnosis and the institution of adequate prophylaxis, in addition to being able to program curative therapy with allogeneic hematopoietic cell transplantation earlier.

Special thanks

The Foundation for Research Support of the State of São Paulo (FAPESP) supported TTF (process n. 2017/04187-9) and ACN (process n. 2016/22158-3). The Hyper IgM Foundation supported TTF and ACN, The Jeffrey Modell Foundation supported ACN.

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No conflicts of interest declared concerning the publication of this article.

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