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Hyper-IgM Syndrome – a case report and a clinical perspective

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KEY WORDS

AICDA, hyper-IgM, hypogammaglobulinemia, immunodeficiency, immunoglobulin M

SUMMARY

The authors describe the case of a 28-year-old woman, with a history of recurrent bacterial infections since childhood and multiple hospitalizations for pneumonia, with important pulmonary sequelae, including bronchiectasis which warranted the need to perform a left lobectomy and lingulectomy at age 13. After diagnostic work up, the diagnosis of hypogammaglobulinemia with hyper-IgM was established, and she began regular replacement IV immunoglobulin treatment, with good tolerance and no side effects. A sequencing of the entire coding region (exons 1-5) of the AICDA gene was performed, and a homozygous c.260G>C mutation was identified, confirming the diagnosis of type 2 hyper-IgM syndrome. This case illustrates the negative impact that a delay in diagnosis and hence delay in treatment has in patients with primary immunodeficiency since early therapy is the only way to reduce the incidence and severity of complications.

Introduction

A 28-year-old woman, with a history of recurrent bacterial infections since childhood and multiple hospitalizations for pneumonia was referred to our outpatient clinic without an established diagnosis. Due to sequelae of the several previous lung infections, with presence of bronchiectasis, she had previously received a left lobectomy and lingulectomy at age 13. She had no relevant family history. The results of a physical examination were unremarkable except for slightly diminished breath sounds in the left side (compatible with her surgical history) and palpable inguinal lymph nodes.

A functional respiratory evaluation was done, revealing an obstructive pattern and pulmonary hyperinflation, with decreased FVC (72% of reference value) and FEV1 (61%

of reference value), a FEV1/FVC ratio of 73%, and an increased RV (164% of reference value) with normal TLC (99% of reference value). Her exhaled nitric oxide was normal. A thoracic computed tomography (CT) scan showed fibrotic lesions and sequelae pleural thickening, left mediastinal shift and multiple cystic and cylindrical bronchiectasis. An inguinal ultrasonography was also done, revealing the presence of reactive lymph nodes, with the largest one having 14x6 mm in diameter.

An analytical study with blood count and routine biochemistry was performed, with normal results. Both the alpha 1-antitrypsin levels and the chloride sweat test were normal. The serum immunoglobulins levels were measured by nephelometry, with IgG <0.08 g/L (N: 6.5-15.0), IgA <0.06 g/L (N: 0.78-3.12), IgM=7.33 g/L (N: 0.55-3.0) and IgE <2 κU/L (N <114). The immunofixa-

tion of serum and urinary proteins showed no monoclonal gammopathy or free light chains in urine.

The diagnosis of hypogammaglobulinemia with hyper-IgM was established, and she began regular replacement IV immunoglobulin treatment (500 mg/kg, every 4 weeks), with good tolerance and no side effects. Until now, approximately 18 months after the diagnosis and beginning of treatment, she has had only a minor respiratory tract infection, with very good response to common antibiotic therapy.

In order to establish a definitive diagnosis regarding subtype of disease, as well as for genetic counselling, a sequencing of the entire coding region (exons 1-5) of the AICDA (activation-induced cytidine deaminase) gene was performed. A homozygous c.260G>C mutation was identified in exon 3 of the AICDA gene, which alters a cysteine into a serine on aminoacid position 87 of the resulting protein (p.Cys87Ser), confirming the diagnosis of type 2 hyper-IgM syndrome.

Discussion/Comments

The hyper-IgM syndrome (HIGM) is one of the rarest primary immunodeficiencies. One registry in Spain reported that the incidence rate of all forms of HIGM is 1 per 20 million live births (1). It is characterized by a deficiency in switching from production of IgM to IgG, IgA and IgE, with the presence of elevated or normal serum IgM levels, and low levels of other immunoglobulin classes. B-lymphocytes can produce IgM antibodies on their own, but they require interaction with T-lymphocytes in order to switch antibody production from IgM to the other immunoglobulin classes. This diagnosis should be considered in any patient presenting with hypogammaglobulinemia, with low or absent IgG and IgA and normal or elevated IgM levels (2).

Most patients with HIGM syndrome develop clinical symptoms during their first or second year of life. The most common problem is an increased susceptibility to infection including recurrent upper and lower respiratory tract infections with encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*) (3).

The HIGM results from a variety of genetic defects that affect this interaction between T and B-lymphocytes. There are 5 main sub-types described, depending on the mutation responsible. The first described, and most common defect, is X-linked hyper IgM syndrome due to deficiency of CD40 ligand (CD40LG), which affects only

male patients. Type 2 has an autosomal recessive inheritance and normal T cell function, and is caused by a mutation in the activation-induced cytidine deaminase (AICDA) gene (3-5), which encodes an enzyme required for the immunoglobulin class-switching process. Type 3 has an autosomal recessive inheritance and is due to a mutation in the CD40 gene. This disorder, as well as type 1, has also an impaired cellular immunity. Type 4 is still poorly known, but the defect seems to be downstream of the AICDA activity. Type 5 has an autosomal recessive inheritance and normal T cell function, and is caused by mutation in the uracil N-glycosylase (UNG) gene (6), which encodes another enzyme required for the process of immunoglobulin class-switching. Since the autosomal recessive forms of HIGM require that the gene on both chromosomes be affected, they are less frequent than the X-linked conditions. Some cases of HIGM syndrome with unknown genetic defects have been reported, including class-switch recombination defects and unclassified HIGM (7, 8).

The final diagnosis of a specific subtype of HIGM depends on the identification of a mutation analysis of the genes known to cause these disorders. This is also important for genetic counselling issues.

All patients with HIGM present with recurrent bacterial infections. Only CD40L defect and CD40 defect are associated with significant T and B cell deficiency, and are also susceptible to opportunistic infections. Lymphoid hyperplasia, caused by the presence of giant germinal centers, is a frequent complication (5). Adenocarcinomas of the liver, biliary tract and other parts of the GI system are another complication of chronic GI disease, and require periodic screening to allow for an early diagnosis. There is also an increased incidence of autoimmune diseases (2, 3). Pulmonary function tests are essential at diagnosis and yearly thereafter to monitor for chronic lung disease. Bronchiectasis is common in patients who experience recurrent episodes of pneumonia. Bacterial pneumonia is mostly preventable using regular IV immunoglobulin replacement therapy.

Replacement IV immunoglobulin is the mainstay of treatment, which not only provides the missing IgG antibodies, but also reduces the IgM antibodies and decreases the recurrence of infections. The lymphoid hyperplasia seems to also improve with this treatment (5). Patients with HIGM, as other patients with primary immunodeficiency diseases, should not receive live virus vaccines. In recent years, bone marrow transplantation has been advocated for the more severe forms of this disease (9).

Key points

- The diagnosis of primary immunodeficiency should be considered in any patient with recurrent childhood infections.
- The hyper-IgM syndrome is characterized by a deficiency in switching from production of IgM to IgG, IgA and IgE, with normal or elevated IgM and low levels of the other immunoglobulin classes.
- All patients with this condition present with recurrent bacterial infections. Lymphoid hyperplasia and autoimmune diseases are a frequent complication. There is also an increased incidence of malignancy of the GI system.
- Replacement IV immunoglobulin is the mainstay of treatment.
- A delay in diagnosis and beginning of replacement therapy is a significant cause of morbidity.

As this case illustrates, a delay in diagnosis can be a significant cause of morbidity, and the diagnosis of primary immunodeficiency must be suspected in patients with recurrent infections since childhood. The early diagnosis and beginning of replacement therapy is the only means to reduce the incidence and severity of complications.

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