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Hyper IgM Syndrome with low IgM and thrombocytosis: an unusual case of Immunodeficiency

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Summary
We report a 5 years old male child with low serum IgG, IgA and IgM levels, who presented with recurrent perianal and oral ulcers, intermittent fever, and protracted diarrhea. Despite the lack of typical respiratory symptoms, low serum IgM level and persistent thrombocytosis, an X-linked hyper-IgM syndrome (X-HIGM) was considered. Laboratory investigations revealed a diagnosis of hyper-IgM syndrome caused by CD40L deficiency.

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The X-linked hyper-immunoglobulin M syndrome (XHIGM) is a rare form of primary immunodeficiency, characterized by hypogammaglobulinemia and impaired cellular immunity. It is caused by several mutations of the CD40 ligand (CD40L), expressed on activated T lymphocytes, resulting in an inability to signal B-cells to undergo isotype switching (1), resulting in markedly reduced levels of IgG, IgA, and IgE with normal or elevated levels of IgM (2).

Male children with CD40L deficiency become symptomatic during early childhood, with recurrent pyogenic infections caused by capsulated or encapsulated bacteria, but they are also more prone to infections with intracellular pathogens such as *Pneumocystis carinii*, *Cryptosporidium parvum,* and *Leishmania.* Other clinical associations may include gastrointestinal ulcers, recurrent or protracted diarrhea, hepatitis, sclerosing cholangitis, neutropenia, thrombocytopenia, and anemia.

Diagnostic criteria (3) used for the US XHIGM registry, the Pan-American Group for Immunodeficiency, and the European Society for Immunodeficiencies, consist of two of the following: 1) mutation of CD40L; 2) a positive family history of a lateral male relative with XHIGM syndrome; and 3) defective expression of CD40L on activated T-lymphocytes. Here we report a case of a 5-year-old boy with defective expression of CD40L with pan-hypogammaglobulinemia including low-normal levels of serum IgM.

A 5-year-old North African boy presented to us with 3 days' history of fever, perianal and oral ulcers, and abdominal pain. His history was significant for multiple admissions due to recurrent perianal and oral ulcers, intermittent fever, and protracted diarrhea. A review of available laboratory data revealed persistent neutropenia and hypogammaglobulinemia, including low levels of IgM. The child was initially diagnosed as a case of congenital neutropenia, Kostman syndrome and hypogammaglobulinemia.

Table 1 *- Summary of immunoglobulin levels (mg/100 ml).*

Immunoglobulin class	Patient levels	Normal range
IgG	230-340	542-1515
IgG1	130-286	380-840
IgG2	69-109	83-543
IgG3	0.6-60	10- 92
IgG4	0.10-0.5	1-11
IgM (obtained 15 times)	29-37 (Except on two occasions when it was 40 and 44 mg/100 ml respectively)	40-230
IgA	45-90	48-301
IgE	< 2 u/l	1.6-30 u/l

Table 2 *- Flow cytometry results.*

Cell type	%	Absolute value
Lymphocytes	44-75%	3894-7300 mm3
CD4+ cells	36-50%	1437-2577 mm3
CD8+cells	14-35%	239-1579 mm3
CD56&CD16 cells	1-7%	1674-244 mm3
MHC Class 1	100%	3939-7300 mm3
MHC class2	20-37%	858-2044 mm3
CD 19+ CD40 cells CD40 L Status	Intact Lack of expression x 3	

A lack of satisfactory clinical response led his parents to contact our tertiary care center. Family history revealed the death of a male sibling at the age of 6 years from severe pneumonia. A review of the brother's medical records revealed hypogammaglobulinemia, albeit, with elevated levels of IgM (2,320 mg/l). The parents were healthy, as were two sisters. Our index patient had multiple admissions due to recurrent oral and severe perianal ulcers, perianal abscess, fever, and protracted diarrhea. The child also had persistent neutropenia and thrombocytosis.

Physical examination, performed during multiple admissions, revealed a similar clinical picture with severe oral and perianal ulcers, hepatosplenomegaly, and abdominal tenderness.

Summary of immunoglobulin levels and flow cytometry results are shown in the **tables 1** and **2**, along with normal ranges reported for pediatric subjects in his age range.

Quantitative analysis of immunoglobulins in serum was low, including IgM (except on two occasions, when it was found to be within normal limits). Flow cytometry results revealed intact CD19 + CD40 cells; however, there was a consistent lack of expression of CD154 (CD40 ligand) on the surface of activated CD4 + lymphocytes. This was repeated three times with similar results. Absolute (ABS) and relative numbers of lymphocyte subsets were normal, excluding the typical cases of severe combined immunodeficiency.

Antibody response to protein and polysaccharide antigens was impaired. Results of lymphocyte stimulation test / blastogenesis revealed a moderate depressed response to mitogens. Levels of complement components measured were elevated: complement C2 was 29.43 mg/l (normal = 4-24 mg/l) and complement CH50 was 662 U/ml (normal = 345-485 g/l).

Other laboratory investigations included: neutropenia, absolute neutrophil count = 0.20-9.2 × 10^9/L (normal = 1.37-7.50 x 10^9) and thrombocytosis, platelet count done multiple times with range of 650-1,344 × 10^9/L (normal = 155-435 x 10^9/L). The platelet counts continued to be elevated despite clinical improvement and normal Erythrocyte Sedimentation rate (ESR) readings between the acute illnesses. Hepatic profile included normal alanine amino transferase 13-35 U/L (normal = 10-35 U/L), aspartate amino transferase 25-27 U/L (normal = 10-45 U/L), and gamma glutamyl transferase 21-27 U/L (normal = 11-49 U/L).

All blood and urine culture results were negative. Peritoneal fluid culture showed many mixed organisms (*Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*, and *Proteus* species). Stool was positive for *Clostridium difficile* toxin during one admission, and stool culture yielded *Salmonella* group D.

Due to lack of an appropriate genetic testing facility in that country, we were unable to obtain mutation analysis on this patient. However, patient was diagnosed with hyper-IgM syndrome due to presence of 2 out of 3 criteria required for the diagnosis of XHIGM (3).

He was continued on intravenous gamma globulin and granulocyte colony stimulating factor and referred to our bone marrow transplant team for possible transplant as a curative therapy.

Although, low IgM in hyper IgM syndrome has been described previously (4). Our index case however, showed deviation from a typical case of hyper-IgM syndrome in the following domains: 1) There has been a consistent low level of IgM except on two occasions (19 out of 21 times). 2) There is a direct correlation

between the platelet count and the concentrations of plasma CD40L (5), a possible explanation of thrombocytopenia in XHIGM. Contrary to expectations, our reported case exhibited persistent thrombocytosis. Iron deficiency, which usually causes thrombocytosis, was ruled out. Extensive review of the literature failed to find any other published report of thrombocytosis in the context of hyper-IgM syndrome / CD40 deficiency. To our knowledge, this is the first case report of CD40L deficiency with low IgM and
thrombocytosis.

3) Lack of respiratory symptoms. *Pneumocystis jirovecii* pneumonia (PCP) is usually the first clinical evidence noted in 59% of XHIGM during early infancy (2). An important consequence of hyper-IgM syndrome is the susceptibility to recurrent infections including *Pneumocystis jirovecii* (43%) (6). Typically, these patients present with respiratory symptoms and pneumonia about 81% of the time (2). However, our patient showed a deviation from this typical clinical pattern.

Conclusions and clinical implication

An important clinical implication is that a diagnosis of hyper IgM syndrome may be missed or delayed in the context of low IgM levels and high platelet counts. This was true in our case, in which a workup for hyper-IgM syndrome was not performed until the age of 4-years because of low IgM levels and thrombocytosis.

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