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*Case Report*

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# Peculiar hyper-IgM syndrome. Case report

## Sindrom hiper-IgM atipic. Prezentare de caz

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## Abstract

*We report a male infant diagnosed at the age of 10 months with hyper-IgM syndrome (HIGM) in context of severe infections caused by Streptococcus pneumoniae, Staphylococcus aureus and Candida albicans. In patient's outcome, in spite of immunoglobulin therapy, he continues presenting bilateral suppurative otitis media due to both Candida and penicillin-resistant pneumococcus and forearm abscess caused by Staphylococcus aureus. The infant developed bilateral cataracts, chronic hepatitis and comminuted fracture secondary to bone demineralization. The patient didn't develop opportunistic infections as compare to CD40 Ligand deficiency patients. In contrast with the majority of HIGM cases, the infant necessity for immunoglobulin substitution was very limited. As a particularity of immunological phenotype, the patient IgM value progressively increased at a high level.*

***Keywords****: hyper-IgM syndrome, severe infections, recurrent infections, bone disease*

## Rezumat

*Autorii raportează cazul unui sugar de sex masculin diagnosticat, la vârsta de 10 luni, cu sindrom hiper-IgM în contextul infecțiilor severe cauzate de Streptococcus pneumoniae, Staphylococcus aureus și Candida albicans. În ciuda terapiei de substituție cu gamaglobulină umană, sugarul a continuat să prezinte frecvente episoade de otită medie supurată cauzate de Candida și pneumococ penicilino-rezistent și abces antebrat determinat de Staphylococcus aureus. În evoluție sugarul a dezvoltat cataractă ambii ochi, hepatită cronică și fractură cominutivă femur secundară demineralizării osoase. Pacientul nu a prezentat infecții cu germeni oportuniști comparativ cu pacienții cu deficiență CD40 Ligand. Spre deosebire de majoritatea bolnavilor cu fenotip hiper-IgM, pacientul a necesitat cantități reduse de gamaglobulină umană. Ca particularitate imunologică, în evoluție valoarea serica a IgM a crescut la valori foarte mari.*

***Cuvinte cheie****: sindrom hiper-IgM, infecții severe, infecții recurente, osteopatie*

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## Introduction

Hyper-IgM syndrome (HIGM) is a rare disease. HIGM patients present normal or high IgM serum levels and markedly decreased serum levels of the other isotypes (IgA, IgG, IgE). The molecular etiologies of HIGM syndromes are: CD40 ligand deficiency, activation-induced cytidine deaminase (AICDA) deficiency, CD40 deficiency, uracil-DNA glycosylase (UNG) deficiency and few NF-kB essential modulator (NEMO)-deficient patients have HIGM phenotype,[1]. Once CD40L – CD40 are connected, the signal transduction will be transmitted in B lymphocytes and dendritic cells, promoting B cell proliferation and starting class switch recombination (CSR) and somatic hypermutation (SHM). The clinical manifestations in CD40L and CD40 deficiencies include opportunistic infections (*Pneumocystis jirovecii*, *Histoplasma capsulatum*, *Cryptosporidium* causing sclerosing cholangitis). Other complications are represented by: neutropenia, thrombocytopenia, Coombs positive hemolytic anemia and osteopenia (suggesting the regulatory role of CD40L in bone mineralization),[2]. AICDA and UNG deficiencies are the result of defects in CSR mechanism. The patients present recurrent (but not opportunistic) bacterial infections and autoimmune diseases. NEMO plays a key role in signal transduction pathway from CD40. NEMO is necessary for NF-kB activation which is involved in various other immunologic pathways (eg. Toll-like-receptors [TLRs], tumor necrosis factor receptor [TNF-R] superfamily member, T-cell receptor [TCR] and B-cell receptor [BCR] pathways) and developmental pathways (eg. pathways with ectodisplasin [EDA], RANK and VEGFR3 required for normal ectodermal, bone and lymphatic development respectively),[3]. Some NEMO-deficient patients displayed ectodermal dysplasia features and only 15% of NEMO-deficient patients displayed a HIGM immunological phenotype [4].

HIGM phenotype was also described in patients with ataxia-teleangiectasia, inducible costimulator deficiency, transmembrane activator and calcium modulating cyclophilin interacting protein deficiency,[3]. Recently, heterozygous gain-of-function mutation in phosphatidyl-inositol-bisphosphate 3-kinase catalytic subunit delta (*PIK3CD*) and phosphoinositide-3-kinase, regulatory subunit 1 alpha (*PIK3R1*) genes causing primary immunodeficiency has been reported,[5,6]. PIK3CD is mandatory for signaling transmission from T and B cell receptors and from other co-stimulatory molecules like TLRs.

The immunologists described undefined genetic background in 6% of patients HIGM-like syndromes,[3].

The therapeutic options for these HIGM syndromes comprise allogeneic hematopoietic stem cell transplantation (HSCT) for CD40L and CD40 deficiencies and also for some NEMO-deficient patients, monthly intravenous immunoglobulin substitution therapy (IVIgG), *Pneumocystis jirovecii* prophylaxis, protection from exposure to *Cryptosporidium* (CD40L and CD40 deficiencies) and granulocyte colony stimulating factor treatment in neutropenia.

## Case report

A 10 months old male infant previously experienced two hospitalizations justified by unilateral *Staphylococcus aureus* otitis media and severe pneumonia.

Family history: the infant was the 4$^{th}$ child in the family and he had three healthy brothers. The parents were apparently healthy and declared as non-consanguineous.

At the time of his first admittance (at 7 months), the physical exam revealed fever, impaired nutritional status (weight < 3$^{rd}$ percentile), coughing, bilateral crackles, unilateral ear canal purulent secretions and the authors considered bronchiolitis and unilateral purulent otitis. Lab-

oratory findings showed: hemoglobin = 12.2 g/dl, white blood cell count (WBC) = 7,300/mm$^3$ (68% neutrophils – 4964/mm$^3$, 20% lymphocytes – 1460/mm$^3$), platelets = 238,000/mm$^3$, C-reactive protein = 55 mg/l (reference range <10 mg/l) and a high transaminase level (ALAT = 74 U/l). Methicillin-sensitive *Staphylococcus aureus* (MSSA) was isolated from ear pus justifying parenteral antibiotics. At 9 months (second hospitalization) the infant was evaluated for fever, coughing dyspnea and unilateral ear canal secretions. Investigations revealed hypo-gammaglobulinemia (gamma fraction in serum protein electrophoresis was 3.7%; total serum proteins 70.9 g/L with reference range 60-80 g/L, immunoglobulins serum levels were not performed), MSSA in ear pus culture and right lung pneumonia based on chest-X ray. The patient received intravenous broad-spectrum antibiotics (Cefuroxime and Gentamicin).

During the third hospitalization (at 10 months), the physical exam showed malnutrition, oral candidiasis (previously not reported), hepatosplenomegaly, no lymph nodes enlargement, bilateral cataracts and bilateral ear canal purulent secretions; microbiological tests confirmed penicillin-resistant pneumococcus (minimum inhibitory concentration > 2 μg/ml) and sensitive-*Candida albicans*. Laboratory investigations revealed: hemoglobin 11.3 g/dl, WBC 11,500 /mm$^3$ (34% neutrophils, 60% lymphocytes); peripheral blood flow cytometry with CD4+ in normal range (34% or absolute count 2,346/mm$^3$), slight B lymphopenia (7% corresponding to 483/mm$^3$, reference range 720–2,600/mm$^3$), T cytotoxic cells lymphopenia (6% corresponding to 414/mm$^3$, reference range 620–2,000/mm$^3$), increased NK cells (42% meaning an absolute count 2,898/mm$^3$, reference range 180–920/mm$^3$). He had normal expressions of CD40 on B cells and CD40 ligand on T lymphocytes (expression of CD40L was comparable to the healthy control); flow cytometry from bone marrow aspirate revealed 3% blasts, 30% B cells precursors and 3% plasma cells. Endomysial antibodies (IgA, IgG) were negative; ALAT = 350 U/l, negative serology for hepatitis A, B, C, Cytomegalovirus, rubella and *Toxoplasma gondii*. He had positive serology for herpes simplex virus types 1 and 2. Epstein-Barr virus quantitative PCR didn't detect EBV-DNA in serum. The parents refused liver biopsy. Bone metabolism evaluation: serum value of 25 hydroxy-vitamin D 29.2 μg/l (reference range 20-70 μg/l); osteocalcin 94.26 ng/ml (reference range 64-70 ng/ml),[7]. Serum immunoglobulins levels showed: IgA 0.05 g/l (reference range 0.17-0.94 g/l), IgG 1.08 g/l (reference range 2.5-11.9 g/l); IgM = 2.28 g/l (reference range 0.41-1.83 g/l), IgE in normal range. Serum α feto-protein was 2.55 ng/ml (reference range 0.89-8.78 ng/ml); normal sweat testing ruled out cystic fibrosis. Microbiological evaluation revealed: sterile urine culture, penicillin-resistant pneumococcus and sensitive *Candida albicans* in ear pus, negative *Cryptosporidium* and *Giardia* antigens from stools. The ophthalmological exam confirmed bilateral cataracts. Antibacterial therapy was initiated (Teicoplanine based on antimicrobial susceptibility test), intravenous antifungal agents (Fluconazole in accordance with antifungigram) and immunoglobulin substitution therapy (400 mg/kg. body weight) were administered, besides pneumocystosis oral prophylaxis. Because of the recurrent otitis media caused by pneumococcus, the patient received 13-valent pneumococcal vaccine (2 doses), without improvement in terms of microbiological outcome (the antibody responses to pneumococcal vaccine weren't tested; there is no international reference material or recognized protective level for pneumococcal antibodies). The cataract was bilaterally solved using phacoemulsification followed by intraocular lens implantation.

The patient's quality of life has remained severely impaired due to bilateral and chronic sup-

purative otitis media and recurrent pneumonia. His evolution was complicated, at 18 months of age, by a rapidly progressive *MSSA* right forearm abscess (etiology microbiologically confirmed after incision and drainage). At 20 months of age, the patient presented spontaneous left femur comminuted fracture, requiring orthopedic intervention and X-ray exam that confirmed bilateral femur demineralization. Up to 20 months of age, IgM serum level has gradually increased to 79.69 g/l and gamma fraction in serum protein electrophoresis reached 50,4% (IgA serum level undetectable, IgG 5.82 g/l, IgM 79.69 g/l) as compared to 3,7% at the time of the second hospitalization.

In order to establish the genetic anomaly responsible for the HIGM phenotype and correlating the genetic assessment to the laboratory findings, CD40 deficiency was excluded by normal CD40 expression on B cells; CD40 ligand, AICDA and UNG deficiencies were eliminated by sequencing the responsible genes (Sanger method was applied for genomic DNA extracted from total blood); no gain-of-function mutations for *PIK3R1* gene or *PIK3CD* gene (E1021K, E525K, N334K, C416R) were identified; ataxia-teleangiectasia was ruled-out based on α feto-protein normal serum range.

## Discussion

HIGM represents a very rare disorder (less than 1 to 1 million population). The patient was considered as genetically undefined HIGM. In contrast to data reporting IgM improvement after starting iv. immunoglobulins substitution therapy, the IgM level increased significantly. According to the IgG threshold (target IgG level has to be maintained over 5 g/l), the patient rarely needed immunoglobulins (from the age of 10 months, the patient received substitution therapy every 3 months). Even though the authors considered the possibility of shorter intervals between immunoglobulin infusions (the replacement therapy is based not only on IgG threshold but also on patient's clinical status), they abstained from substitution therapy because of the rapid growing of serum IgG. The chronic liver disease could be explained by herpes virus infection or antibacterial therapy. Even though the pathogenic mechanism of bone demineralization was previously described in CD40L deficiency [2], the authors can't attribute the same mechanism to this case. The high risk for hyperviscosity syndrome (hypergammaglobulinemia) justified the maintenance of optimal patient hydration and plasmapheresis option. Concerning HSCT, the authors do not consider it as an emergency due to potential spontaneous remission,[8] so for the moment, transplant option remains questionable.

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## Competing interests

The authors have no conflicts of interest to disclose.

## Contributorship statement

ISI conceived the article based on clinical and therapeutic particularities of the clinical case. ISI and CP drafted the paper. CP and LM contributed to genetic testing of the patient. CP evaluated the article for its improvement.

## Abbreviations

AICDA = activation-induced cytidine deaminase;
CD40L = CD40 ligand;

EBV = Epstein-Barr virus;
HIGM = hyper-IgM syndrome;
MSSA = Methicillin-sensitive Staphylococcus aureus;
NEMO = NF-kB essential modulator;
UNG = uracil-DNA glycosylase;
PCR = polymerase chain reaction;
PIK3CD = phosphatidyl-inositol-bisphosphate 3-kinase catalytic subunit delta;
PIK3R1 = phosphoinositide-3-kinase, regulatory subunit 1 alpha;
TLR = Toll like-receptors;
TNF-R = tumor necrosis factor receptor.

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