**CASE REPORT**
Iran J Allergy Asthma Immunol
March 2008; 7(1): 41-44

# Onychomadesis in a Patient with Immunoglobulin Class Switch Recombination Deficiency

**Mojgan Safari[1], Nima Rezaei[2], Mehrdad Hajilooi[3], Asghar Aghamohammadi[2], Qiang Pan-Hammarstrom[4], and Lennart Hammarstrom[4]**

*[1] Clinical Immunology and Allergy Department, Pediatric Ward, Besat Hospital, Hamadan University of Medical Sciences, Hamadan, Iran*
*[2] Immunology, Asthma and Allergy Research Institute, Medical Sciences/ University of Tehran, Tehran, Iran*
*[3] Department of Immunology, Hamadan University of Medical Sciences, Hamadan, Iran*
*[4] Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute at the Karolinska University Hospital, Stockholm, Sweden*

***Received: 19 August 2007; Received in revised form: 21 September 2007; Accepted: 5 October 2007***

## ABSTRACT

Immunoglobulin class switch recombination deficiencies (Ig CSR deficiencies) or Hyper IgM syndromes (HIGM) are a group of primary immunodeficiency diseases, characterized by defective CD40 signaling of B cells, resulting in reduced CSR and somatic hypermutation. The affected patients are characterized by low serum levels of IgG and IgA, and normal or elevated levels of IgM, which lead to an increased susceptibility to infections.

We describe a 3 year-old boy with frequent bacterial infections of the skin and respiratory tract, mucosal ulcers, and diarrhea. He experienced onychomadesis of both fingernails and toenails during a recent bacterial infection. Quantitative immunoglobulin measurements revealed high levels of serum IgM and very low levels of IgG, IgA, and IgE. Clinical and immunologic studies supported the diagnosis of HIGM.

Exclusion of CD40L, CD40, AID and UNG genes by molecular analysis in this patient may suggest a new form of selective CSR deficiency.

**Key words:** Class switch recombination; Hyper IgM syndrome; Nail shedding; Onychomadesis

## INTRODUCTION

Immunoglobulin class switch recombination deficiencies (Ig CSR deficiencies) or Hyper-IgM syndromes (HIGM) is a primary immunodeficiency disease, which were first described in 1961.[1-3] Affected patients are characterized by reduced serum levels of IgG, IgA and IgE levels, and normal or elevated IgM levels, leading to recurrent and chronic bacterial infections. While the exact pathophysiology of the disease is still unclear, it seems that the B lymphocytes of the patients have an intrinsic inability to undergo

**Corresponding Author:** Mojgan Safari, MD;
Pediatric Ward, Besat Hospital, Hamadan, Iran. Tel: (+98 918) 312 1760, Fax: (+98 811) 264 0064, E-mail: mo_sfr@yahoo.com

immunoglobulin isotype switching.[4] T lymphocyte defects in some types of HIGM could also make the patients prone to opportunistic infections.[5]

Five different genetic defects leading to HIGM have been introduced till now.[6,7] The most common form of disease is the X-linked form, which is caused by mutations of the *CD40 ligand* (*CD40L*). Mutations of *CD40*, the receptor for CD40L, could cause a rare autosomal form of disease with a similar clinical phenotype as the patients with CD40L deficiency. Mutations of *Activation-Induced Cytidine Deaminase* (*AICDA*) and *Uracil-DNA Glycosylase* (*UNG*), lead to defective Ig CSR deficiencies due to intrinsic B-cell defects. The clinical spectrum and the prognosis of the various defects of Ig CSR deficiencies differ; thus CD40L and CD40 deficiencies are classified as combined immunodeficiencies whereas AID and UNG deficiencies are predominantly antibody deficiencies.[7] Mutations in *Nuclear Factor κB Essential Modulator* (*NEMO*) could also lead to an X-linked disease which is associated with hypohidrotic ectodermal dysplasia, and increased levels of IgM.[6]

Herein we describe a case of HIGM who presented with onychomadesis.

## CASE REPORT

A 3-year old boy was admitted in Ekbatan Hospital affiliated to Hamedan University of Medical Sciences for investigation because of frequent infections. His problems started from 5 months of age with bacterial otitis media. Then, he experienced frequent infections including otitis media, pharyngitis, gingivitis, pneumonia, sinusitis and skin infections. He suffered from oral and perianal ulcers periodically (Table 1). He had frequent courses of treatments with antibiotics. He had no problem after vaccine administration. There was no positive family history of immunodeficiency diseases, malignancies or rheumatologic diseases.

His growth and development were normal. However, his fingernails and toenails were shedded completely in the course of a febrile disease about 10 days before hospitalization. Immunologic evaluation revealed very low levels of serum IgG, IgA and IgE (IgG = 90 mg/dl, IgA = 2 mg/dl, IgE = 3 IU/dl) and normal level of serum IgM (IgM= 201 mg/dl). The relative proportions of immune cells were 27% of CD4, 35% of CD8, and 19% of CD19. CH50 was normal.

**Table 1. Clinical and laboratory data of the 3-year old boy with hyper IgM syndrome.**

| | |
|---|---|
| Clinical manifestations | Otitis media |
| | Pharyngitis |
| | Gingivitis |
| | Pneumonia |
| | Sinusitis |
| | Skin infections |
| | Onychomadesis |
| | Oral and perianal ulcers |
| Immunological data | IgG = 90 mg/dl |
| | IgA = 2 mg/dl |
| | IgE = 3 IU/dl |
| | IgM= 201 mg/dl |
| | T-cell CD3+= 62% |
| | T-cell CD3+CD4+= 27% |
| | T-cell CD3+CD8+= 35% |
| | B-cell CD3+CD19+= 19% |
| | CH50 = Normal |
| Hematological data | WBC= 3100 cells/$mm^3$ |
| | PMN= 10% |
| | Lymphocytes= 88% |
| | Eosinophils= 1% |
| | Monocytes= 1% |

Hematological examination revealed severe neutropenia (WBC= 3100 cells/$mm^3$, PMN= 10%, lymphocytes= 88%, eosinophils= 1%, monocytes= 1%) (Table 1). Clinical and immunologic studies supported a diagnosis of HIGM. In the genetic studies, coding regions of *CD40L*, *CD40, AID* and *UNG* were normal.

The patient improved with antibiotic and IVIG therapy. On a regimen of monthly IVIG infusion and oral trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis jiroveci* pneumonia, the patient showed no recurrent infections. Growth of normal nails started 3 weeks after shedding.

## DISCUSSION

Clinical manifestations and immunologic findings of the presented case strongly supported the diagnosis of HIGM. Recurrent respiratory tract infections, chronic diarrhea are common clinical manifestations of disease, followed by oral ulcers, sclerosing cholangitis, hepatitis, arthritis, meningoencephalitis, and malignancies.[8,9] As patients with CD40L deficiency are

susceptible to interstitial pneumonia caused by *Pneumocyctis jiroveci*, such a diagnosis was considered for this patient; Although the *CD40L* gene was intact, we cannot exclude mutations in the promoter region of CD40L, as it was not investigated. Moreover, the patient has neutropenia, which is frequently reported in patients with CD40L deficieny.[10-12] While the clinical diagnosis of CD40L deficiency has to be confirmed by evaluation of the CD40L expression by flow cytometry,[13] the final molecular diagnosis depends on sequence analysis using cDNA or genomic DNA.[6]

Intranvenous immunoglobulin replacement therapy and prophylactic co-trimoxazole should be considered in the treatment protocol. Granulocyte-colony stimulating factor may help improve the neutropenia.[13] As there may be a poor prognosis for the patients, despite optimal medical treatment, hematopoietic stem cell transplantation and liver transplantation, in the cases with advanced liver disease, could also be considered.[14,15]

The patient's fingernails and toenails had shed completely at the first visit, but skin, hair, and teeth were intact. Furthermore, the function of sweat glands was also normal. Thus a defect in NEMO is unlikely but cannot be excluded. Growth of normal nails started 3 weeks after shedding. These findings supported a diagnosis of onychomadesis, which is defined as spontaneous separation of the nail plate from the nail bed, beginning at its proximal end and resulting in shedding of the nail.[16] Although it is a rare condition in children,[17] it has been shown to be associated with a variety of clinical settings such as systemic illnesses, generalized skin diseases, and various form of drug therapy.[16] Spontaneous complete healing of the nails is usually seen within a few weeks.[17]

It seems that a febrile disease appeared as the stressful event preceding onychomadesis in our patient. As the coding regions *CD40L*, *CD40*, *AID* and *UNG*, genes that known to be responsible for HIGM, were intact in this case, a new form of CSR deficiency may be suspected. However, mutations in the promoter region of *CD40L* remain to be excluded.

## ACKNOWLEDGEMENTS

The authors would like to thank Dr. Anne Durandy, Hopital Necker-Enfants Malades (Paris, France), for her kind help in analysis of the UNG gene in this patient.

## REFERENCES

1. Rosen FS, Kevy SV, Merler E, Janeway CA, Gitlin D. Recurrent bacterial infections and dysgamma-globulinemia: deficiency of 7S gamma-globulins in the presence of elevated 19S gamma-globulins. Report of two cases. Pediatrics 1961; 28:182-95.
2. Burtin P. An example of atypical agammaglobulinemia (a case of severe hypogammaglobulinemia with increase of the beta-2 macroglobulin. Rev Fr Etud Clin Biol 1961; 6:286-9.
3. Cooper MD, Faulk WP, Fudenberg HH, Good RA, Hitzig W, Kunkel HG, et al. Meeting report of the Second International Workshop on Primary Immunodeficiency Disease in Man held in St. Petersburg, Florida, February, 1973. Clin Immunol Immunopathol 1974; 2(3):416-45.
4. Notarangelo LD, Duse M, Ugazio AG. Immunodeficiency with hyper-IgM (HIM). Immunodefic Rev 1992; 3(2):101-21.
5. Mayer L, Kwan SP, Thompson C, Ko HS, Chiorazzi N, Waldmann T, et al. Evidence for a defect in "switch" T cells in patients with immunodeficiency and hyperimmunoglobulinemia M. N Engl J Med 1986;314(7):409-13.
6. Etzioni A, Ochs HD. The Hyper IgM Syndrome--an Evolving Story. Pediatr Res 2004; 56(4):519-25.
7. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, et al; Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007; 120(4):776-94.
8. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, et al. Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr 1997; 131(1 Pt 1):47-54.
9. Notarangelo LD, Hayward AR. X-linked immunodeficiency with hyper-IgM (XHIM). Clin Exp Immunol 2000; 120(3):399-405.
10. Rezaei N, Farhoudi A, Pourpak Z, Aghamohammadi A, Moin M, Movahedi M, et al. Neutropenia in Iranian patients with primary immunodeficiency disorders. Haematologica 2005; 90(4):554-6.
11. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, et al. Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol 2006; 26(6):519-32.

12. Atarod L, Aghamohammadi1 A, Moin M, Kanegane H, Rezaei N, Rezaei Kalantari K, et al. Successful management of neutropenia in a patient with CD40 ligand deficiency by immunoglobulin replacement therapy. Iran J Allergy Asthma Immunol 2007; 6(1):37-40.
13. Ravanbakhsh M, Sarafnejad A, Aghamohammadi A, Kardar GA, Asgarian Omran H, Atarod L, et al. CD40 ligand expression on stimulated T-helper lymphocytes in patients with common variable immunodeficiency. Iran J Allergy Asthma Immunol 2007; 6(3):129-35.
14. Khawaja K, Gennery AR, Flood TJ, Abinun M, Cant AJ. Bone marrow transplantation for CD40 ligand deficiency: a single centre experience. Arch Dis Child 2001; 84(6):508-11.
15. Hadzić N, Pagliuca A, Rela M, Portmann B, Jones A, Veys P, et al. Correction of the hyper-IgM syndrome after liver and bone marrow transplantation. N Engl J Med 2000; 342(5):320-4.
16. Mehra A, Murphy RJ, Wilson BB. Idiopathic familial onychomadesis. J Am Acad Dermatol 2000; 43(2 Pt 2):349-50.
17. Bernier V, Labreze C, Bury FA. Nail matrix arrest in the course of hand, foot and mouth disease. Eur J Pediatr 2001; 160(11):649-51.