

## CASE REPORT

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# Autosomal Recessive Chronic Granulomatous Disease, IgA Deficiency and Refractory Autoimmune Thrombocytopenia Responding to Anti-CD20 Monoclonal Antibody

Bibi Shahin Shamsian<sup>1</sup>, Davoud Mansouri<sup>2</sup>, Zahra Pourpak<sup>3</sup>, Nima Rezaei<sup>3</sup>, Zahra Chavoshzadeh<sup>1</sup>, Farzaneh Jadali<sup>1</sup>, Atoosa Gharib<sup>1</sup>, Samin Alavi<sup>1</sup>, Aziz Eghbali<sup>1</sup>, and Mohammad Taghi Arzanian<sup>1</sup>

<sup>1</sup> Department of Pediatric Hematology-Oncology, Immunology, Pathology, Mofid Children's Hospital, Tehran, Iran

<sup>2</sup> National Research Institute of Tuberculosis and Lung Disease, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup> Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran

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## ABSTRACT

Immunodeficiency and autoimmune disease may occur concomitantly in the same individual. Some of the immunodeficiency syndromes, especially humoral defects are associated with autoimmune disorders. Hematological manifestations such as thrombocytopenia and hemolytic anemia are the most common presentations. Persistent antigen stimulation due to an inherent defect in the ability of the immune system to eradicate pathogens is the primary cause leading to autoimmunity in patients with primary immunodeficiency states.

We describe a 10 year old Iranian girl with chronic granulomatous disease -the autosomal recessive type with mutation of *NCF1* gene P47- associated with selective IgA deficiency, refractory immune thrombocytopenia that showed an excellent response to Rituximab (Anti-CD20 monoclonal antibody).

Patients with primary immunodeficiencies may have variable autoimmune manifestations. So for early detection and appropriate treatment, autoimmune diseases should always be suspected in such patients.

**Key words:** Anti-CD20; Autoimmune thrombocytopenia; Chronic granulomatous disease; IgA deficiency; Primary immunodeficiency diseases

## INTRODUCTION

Primary immunodeficiency diseases (PID) are heterogeneous group of disorders, characterized by increased susceptibility to recurrent infections as well as malignancies and autoimmune diseases.<sup>1-4</sup>

Selective IgA deficiency (SIgAD) is one of the most common types of PID, characterized by low serum levels of IgA (<5 mg/dL) in the presence of normal IgG and IgM.<sup>1</sup> The incidence of autoimmune disease in SIgAD varies between 7% and 36%.<sup>4</sup>

Chronic granulomatous disease (CGD) is another type of the PID, involving the reduced nicotinamide dinucleotide phosphate (NADPH) oxidase complex which lead to a defect in ability of the bacterial killing by neutrophils, especially catalase-positive bacteria and fungi. CGD consists of a group of X-linked (60%) and

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**Corresponding Author:** Bibi Shahin Shamsian, MD;  
Departments of Pediatric Hematology-Oncology, Mofid Children's Hospital, Shariati Ave, Tehran, Iran. Tel: (+98 21) 2222 7020, Fax: (+98 21) 2222 0254, E-mail: shamsianb@yahoo.com

autosomal recessive (40%) conditions.<sup>5</sup> The pathogenesis of autoimmunity in PID is multifactorial, including T-cells regulation defect, abnormal apoptosis, and abnormal production of immunoglobulins with autoimmune features.<sup>4</sup> The most common immune hematological manifestations are autoimmune thrombocytopenic purpura and immune hemolytic anemia, which are particularly common in patients with antibody defects such as common variable immunodeficiency (CVID) and SIgAD.<sup>4,6</sup> Corticosteroids, intravenous immunoglobulin (IVIG), splenectomy, and Rituximab (Anti-CD20 monoclonal antibody) could be considered for treatment of such conditions.<sup>7-11</sup>

In this article, an Iranian girl with CGD associated with SIgAD is described, who had refractory autoimmune thrombocytopenia responding to rituximab.

### CASE REPORT

The patient was a 10-year old Iranian girl, the second child of first-cousins parents. There was a history of CGD in her elder sister resulting in death. Her disease began one year before admission (2006), when she experienced respiratory infection and refractory lung disease. The laboratory tests are presented in Table 1. The serum level of IgA was rechecked and the low value was confirmed. The nitro blue tetrazolium (NBT) and dihydroxyrhodamin (DHR) tests of parents were in normal range. Western blot test for CGD subtyping showed absence of P47 protein. Polymerase chain reaction (PCR) and sequencing analysis of the encoding gene showed mutation in *NCF1* gene (null mutation) and the diagnosis of autosomal recessive form of CGD was established. After treatment of her lung infection and recovery, prophylaxis with cotrimoxazol and itraconazol started. She was well till 6 month later. This time her platelet count dropped down to 20000/mm<sup>3</sup> with clinical manifestations of nasal bleeding, petechiae and ecchymoses. The reticulocyte count was 2% and her direct and indirect coombs tests were negative. The collagen vascular tests were normal. HBs Ag was negative and Anti-HBs antibody titer was >100mIU/ml, Anti-HCV and Anti-HIV antibodies were negative. Liver function tests, PT and PTT were normal. Her bone marrow aspiration showed no abnormality except an increase in megakaryocytes. Cytogenetic study was

normal. The patient was treated with corticosteroid and IVIG. The platelet number increased, but after discontinuation of corticosteroid the platelet count dropped again. Treatment with these drugs was repeated, but the responses were transient. Several months later, the patient was admitted in another center due to intracranial hemorrhage with a platelet count of 28000/mm<sup>3</sup>. Craniotomy was performed. She had mild degrees of left hemiparesis after intracranial hemorrhage. Because of her underlying disease posing a high risk of severe infections and mortality, splenectomy was not possible in spite of her persistent thrombocytopenia (last platelet count: 14000/mm<sup>3</sup>).

Treatment with cyclosporine A (5-7 mg/kg/day) was not effective either. Consequently, treatment with rituximab (375mg/m<sup>2</sup> /week ×4 weeks) was started. The platelet count increased to 223000/mm<sup>3</sup> after the first dose of rituximab. Now, after 8 months of treatment -with administration of 4 doses of rituximab- the patient has a good condition.

The results of her last tests are as follows; WBC count: 5600/mm<sup>3</sup>, Hb: 13.5 gr/dl, Platelet: 327000/mm<sup>3</sup>. IgG: 1380 mg/dl (700-1600), IgA: 7 mg/dl (70-400), IgM: 111 mg/dl (40-230), IgE: 2.7 IU/ml (<20). The liver and kidney function tests are normal. She is on prophylaxis with cotrimoxazol and itraconazol.

**Table 1. Laboratory data of the case with CGD and IgA deficiency before beginning of Immune thrombocytopenia purpura (ITP)**

Tests	Result
<b>CBC</b>	
- WBC count	8000 cell/mm <sup>3</sup>
- RBC count	4600000 cell/mm <sup>3</sup>
- Hb	10 gr/dL
- Platelet count	335000 cell/mm <sup>3</sup>
<b>Immunoglobulins</b>	
- IgG	2200 mg/dL
- IgM	108 mg/dL
- IgA	3 mg/dL
Nitro blue tetrazolium (NBT)	0 (90-100%) control: 100%
Dihydroxyrhodamin tests (DHR)	9.44 (50-200) control: 214%
<b>Flowcytometry</b>	
- CD3	61.2%
- CD4	37%
- CD8	30%
- CD19	21.5%

### DISCUSSION

Although immunodeficiency and autoimmunity states seem to be the opposite sides in the spectrum of the clinical immune response theoretically, these two conditions are frequently related. Immunodeficiency and autoimmune phenomena may occur concomitantly in the same individual. Many PID diseases such as SIgAD and CVID are associated with autoimmune hematological manifestations.<sup>3,4,12</sup>

Due to the persistent infections, patients with CGD could have high levels of immunoglobulins with several autoantibodies.<sup>4</sup> More than 15% of the children with CGD suffer from autoimmune diseases such as Crohn and discoid lupus erythematosus.<sup>4</sup> Coexistence of two PID (CGD and SIgAD) is an interesting issue that is very rare. Sieber *et al* reported a 6.5-year old boy with CGD and SIgAD with chronic progressive pneumonia caused by *Pseudomonas cepacia*.<sup>13</sup> Gerba *et al* reported a case of CGD and SIgAD with multiple autoantibodies and progressive pulmonary dysfunction.<sup>14</sup> Jacek *et al* reported a case of CGD and refractory autoimmune thrombocytopenia in a girl which was successfully treated with cyclosporine A and rituximab. Our patient had coexistence of CGD, SIgAD and refractory immune thrombocytopenic purpura who developed intracranial hemorrhage. As to the probable cause of the patient's thrombocytopenia, it should be noted that numerous drugs have been implicated as the causes of antibody mediated thrombocytopenia. Sulfamethoxazole is one of the more common causes of drug-induced thrombocytopenia in children, but this type of thrombocytopenia usually resolves when the drug is discontinued. Thrombocytopenia in our patient could not be due to drug-induced thrombocytopenia, because our patient did not take her drugs persistently and also that after discontinuation of cotrimoxazol, thrombocytopenia did not resolve.

The underlying mechanism of an immune hematological disease in PID is complex. The inability of defective immune system to eradicate microbial and viral pathogens could result in a compensatory, aggravated chronic inflammatory response, leading to ongoing tissue damage. In our case the usual treatment of immune thrombocytopenic purpura, including corticosteroids and intravenous immunoglobulin, were not effective. The response to cyclosporine A was not very good, but the trial of rituximab 375 mg/m<sup>2</sup>/week

× 4 weeks resulted in complete response. Rituximab is a humanized mouse monoclonal antibody against the B-lymphocyte surface antigen CD20 which elicits a therapeutic response in patients with chronic ITP.<sup>15</sup> The use of this drug in patients with ITP produces long-term responses, which are usually associated with a sustained B cell depletion and a decrease or disappearance of anti-platelet antibodies. Recently, Stasi *et al* showed that this response was associated with significant changes of T-cell compartment.<sup>8</sup>

The patients with PID could have variable autoimmune manifestations. Therefore autoimmune diseases should always be suspected in such patients, for early detection and appropriate treatment. In patients with PID, rituximab can be a clinically effective treatment for hematologic manifestations such as immune thrombocytopenic purpura and immune hemolytic anemia.<sup>1,9-14</sup>

### REFERENCES

1. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin Immunol* 1999; 93(3):190-7.
2. Sarmiento E, Mora R, Rodríguez-Mahou M, Rodríguez-Molina J, Fernández-Cruz E, Carbone J. Autoimmune disease in primary antibody deficiencies. *Allergol Immunopathol (Madr)* 2005; 33(2):69-73.
3. 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.
4. Etzioni A. Immune deficiency and autoimmunity. *Autoimmun Rev* 2003; 2(6):364-9.
5. Movahedi M, Aghamohammadi A, Rezaei N, Shahnava N, Jandaghi AB, Farhodi A, et al. Chronic granulomatous disease: a clinical survey of 41 patients from the Iranian primary immunodeficiency registry. *Int Arch Allergy Immunol* 2004; 134(3):253-9.
6. De la Concha EG, Subiza JL, Fontán G, Pascual-Salcedo D, Sequi J, Bootello A. Disorders of regulatory T cells in patients with selective IgA deficiency and its relationship to associated autoimmune phenomena. *Clin Exp Immunol* 1982; 49(2):410-8.
7. Treliński J, Chojnowski K, Kurenko-Deptuch M, Kasznicki M, Bernatowska E, Robak T. Successful

- treatment of refractory autoimmune thrombocytopenia with rituximab and cyclosporin A in a patient with chronic granulomatous disease. *Ann Hematol* 2005;84(12):835-6.
8. Stasi R, Del Poeta G, Stipa E, Evangelista ML, Trawinska MM, Cooper N, et al. Response to B-cell depleting therapy with rituximab reverts the abnormalities of T cell subsets in patients with idiopathic thrombocytopenic purpura. *Blood* 2007; 110(8):2924-30.
  9. Bay A, Oner AF, Uner A, Dogan M. Use of rituximab in chronic childhood immune thrombocytopenic purpura. *Case Reports. Pediatr Int* 2006; 48(5):514-6.
  10. Park CY, Chung CH. A patient with mixed type Evans syndrome: efficacy of rituximab treatment. *J Korean Med Sci* 2006; 21(6):1115-6.
  11. El-Shanawany TM, Williams PE, Jolles S. Response of refractory ITP in a patient with common variable immunodeficiency (CVID) to treatment with rituximab. *J Clin Pathol* 2007; 60(6):715-6.
  12. Ramyar A, Aghamohammadi A, Moazzami K, Rezaei N, Yeganeh M, Cheraghi T, et al. Presence of idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia in the patients with common variable immunodeficiency. *Iran J Allergy Asthma Immunol* 2008; 7(3):169-75.
  13. Sieber OF, Fulginiti VA. *Pseudomonas cepacia* pneumonia in a child with chronic granulomatous disease and selective IgA deficiency. *Acta Paediatr Scand* 1976; 65(4):519-20.
  14. Gerba WM, Miller DR, Pahwa S, Cunningham-Rundles C, Gupta S. Chronic granulomatous disease and selective IgA deficiency. *Am J Pediatr Hematol Oncol* 1982; 4(2):155-60.
  15. Nathan DG, Orkin SH, A. Look T, Ginsburg D. Nathan and Oski's hematology of infancy and childhood. London: WB Saunders, 2003: 1597-608.