OXFORD

Oxford Medical Case Reports, 2022, **5**, 205–207
https://doi.org/10.1093/omcr/omac055
Case Report

A rare case of combined immunodeficiency with cytopenia whose symptoms were controlled by cyclosporine

Bazgir Narges[1], Eskandarzadeh Shabnam[2], Eslamian Golnaz[2], Chavoshzadeh Zahra[2], Shah Jaffer[3] and Qaderi Shohra[4,*]

[1]Department of Internal Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Allergy and Clinical Immunology, Shahid Beheshti University of Medical Sciences
[3]Drexel University College of Medicine, Pennsylvania 19104, USA
[4]Medical Research Center, Kateb University

*Correspondence address. Kabul 0093, Afghanistan. Fax: 00982177551023; E-mail: Shohra_qaderi@yahoo.com

Abstract

Combined Immunodeficiency (CID) is a group of inborn error of Immunity (IEI) that may present with both infectious and non-infectious complications. Autoimmunity is an unusual presentation of CID and can be presented as cytopenia. The initial management of cytopenia is corticosteroids and IVIG. The role of other cytotoxic and immunosuppressive drugs in management of cytopenia is not fully understood. The objective of this clinical case report is to highlight the possibly beneficial role of cyclosporine in controlling cytopenia in CID patients. A 26-month-old child with generalized ecchymosis was referred to Mofid Children's Hospital in Tehran, Iran. Physical examination revealed no substantial findings other than ecchymosis, and complete blood count (CBC) revealed thrombocytopenia. Diagnosis of CID and cytopenia followed. The patient was treated by 5 times prednisolone and 4 times Rituximab. Finally, his ecchymosis was controlled by Cellcept, which was then tempered and substituted by cyclosporine.

INTRODUCTION

Combined immunodeficiency (CID) is a heterogeneous and genetic groups of diseases which effect the immune system. It is known as a primary immunodeficiency (PID). Classically, PID is categorized into two main groups—adaptive and innate immune disorders [1]. The initial management of CID-associated cytopenia is comprised of empirical management. Corticosteroids (Corticosteroids (steroids; a type of anti-inflammatory drug)), anti-D Anti-Rhesus (neutralizes any RhD positive antigens), intravenous immunoglobulin (IVIg), and eventually splenectomy, have all been used to treat cytopenia associated with immunodeficiency. Corticosteroids are the first-line treatment used to cure CID-associated cytopenia and to successfully manage its initial symptoms. For intractable and chronic cases—especially in immune thrombocytopenia (ITP), splenectomy is sometimes indicated [2]. The benefits and side effects of cytotoxic (cyclophosphamide) and immunosuppressive drugs are not clear [2]. Cyclosporine is an immunomodulatory drug. Cyclosporine is rarely used to manage the cytopenia in CID patients. Usually, CID patients respond to the aforementioned therapies. We report a complicated CID case with cytopenia whose symptoms were successfully controlled by cyclosporine.

CASE REPORT

A 2-year-and-2-month-old male child was referred to Mofid Children's Hospital due to recurrent pulmonary infection and diarrhea. He is the third child of a consanguineous parent. His younger sister was a suspected CID case who was treated with IVIG. The vaccination history was based on national instruction. The patient was neurologically and developmentally normal. He was hospitalized in another center multiple times before being referred to this center. From 7 months, until 1 year and 3 months old, he was observed and controlled for a food allergy. He was rehospitalized 6 months later due to fever, long-lasting oral aphthous, erosions, candida infection and erythema around his mouth and anus. Endoscopy was normal. Recurrent sinus infection, pneumonia within a year and >2 months of oral antibiotic use with little effects lead to an immunodeficiency suspicion. Immunological workup was performed, revealing low levels of immunoglobulin G and immunoglobulin M. Enzyme-linked immunoabsorbed assays were used to analyze anti-tetanus and anti-diphtheria immunoglobulin titers. Enzyme linked immunoabsorbed assays were used to analyze anti-tetanus, and anti-diphtheria immunoglobulin titer which both specific antibody concentrations were not above 0.1 needed to demonstrate

Received: September 1, 2021. **Revised:** February 17, 2022. **Accepted:** April 25, 2022

Table 1. Hematologic changes and medicine prescribed for the patient

WBC (/L)	RBC (/L)	Hb (g/dl)	HCT (%)	MCV (fl)	PLT (/L)	Medication
8800 (L = 63, N = 29)	3.51*10^6	10.2	29.9	85.2	303 000	methylprednisolone + 3*Platlate
6300 (L = 62, N = 62)	3.6*10^6	10	29	80.56	2000	Methylprednisolone
6100 (L = 35, N = 57)	4.14*10^6	11.7	34	83.8	8000	Rituximab
4000 (L = 18, N = 78)	4.2*10^6	12	36	85.71	1000	Rituximab
9000 (N = 69.8, L = 21.3)	4.01*10^6	11.4	34.3	85.54	26 000	Cellcept
5900 (L = 15, N = 78)	3.84*10^6	10.9	33.1	85.5	23 000	Cellcept
6900 (L = 14, N = 80)	5*10^6	12.7	38.5	77	151 000	Cyclosporine

RBC = red blood cell, Hb = hemoglobin, HCT = hematocrit, MCV = mean cell volume, PLT = platelet, L = lymphocyte percentage, N = neutrophil percentage.

protection. In addition, a lymphocyte transformation test (LTT) was performed. Phytohemagglutinin, Bacillus Calmette-Guérin and candida were all abnormal. His CBC revealed a decrease in the number of white blood cells (WBC = 4600). Eventually, based on low levels of immunoglobulins, the flow cytometry test revealing low CD4 and CD8 cell % count, recurrent infections and abnormal LTT, he was considered to be a case of CID. He was discharged with daily antibiotic prophylaxis and vitamin supplements. A single dose of 10 mg of IVIG was also considered monthly. At the age of 2 years and 2 months, he was admitted because of generalized ecchymosis. Physical examination revealed generalized ecchymosis but was otherwise normal. His CBC with differential showed lymphopenia and thrombocytopenia (platelet count = 19 000). Bone marrow aspiration was performed for him. There was no evidence of bone marrow failure in bone marrow aspiration. Cytomegalovirus and Ebstein-Barr virus deoxyribonucleic acid was not detected in plasma. Consequently, he was diagnosed with ITP. In order to control his ITP, he received three doses of methylprednisolone pulses and three platelet infusions (Table 1). He received rituximab four times. Platelet count did not respond to the aforementioned drugs. As a result, mycophenolate mofetil, also known by its brand name, 'Cellcept' was prescribed. Since thrombocytopenia was evident, Cellcept was administered. His last platelet count was 47 000 after receiving platelets and Cellcept. His ecchymosis was controlled and relieved by Cellcept, and only a 3∗2-cm ecchymosis remained on his waist. Cellcept was tapered and substituted by cyclosporine. Liver function test, electrolytes and lipid profile were normal. Computed tomography (CT) scan of paranasal sinuses demonstrated mucosal thickening of all paranasal sinuses and a small concha bullosa with left adenoid hypertrophy. Ground glass opacity of both upper lobes and interlobular septal thickening in a spiral thorax CT scan suggested atypical lung infection. His lung infection was properly controlled. The patient was discharged with prednisolone 5 mg every 6 hours, cyclosporine 13 mg daily, fluconazole 5 mg daily, folic acid 1 g every other day, ferrous sulfate 30 mg, folic acid and 10 mg IVIG every 30 days. One month after discharge, he visited clinic again. His platelet had reached 155 000. Thereafter, following frequent visits, his platelet levels never dropped again. Thus, his ITP was successfully controlled by cyclosporine.

DISCUSSION

Cytopenias evolve in ∼50% of T-cell deficiencies (CID) in older patients and in 10–30% of children under the age of 18 [3]. The most common way to address CID symptoms involves supportive care measures, aggressive management of established infection, immunoglobulin replacement, prophylactic antibiotic and anti-fungal and immunosuppressive drugs, among which, corticosteroids are most commonly used. Other drugs, such as rituximab and IVIG have been used successfully [1, 4]. Nowadays, monoclonal antibodies and cytokine inhibitors are used more instead of immunosuppressive and immunomodulating agents in order to control symptoms [5]. Steroids are commonly used as first-line treatment of immunodeficiency cytopenia and are often effective. However, the complete resolution of symptoms depends on successful hematopoietic stem cell transplantation, bone marrow transplant or gene therapy [1]. Corticosteroids control autoimmune hemolytic anemia, while IVIG and danazole are the first-line treatment for thrombocytopenia [6, 7]. Corticosteroids and anti-D are prescribed to treat thrombocytopenia in immunodeficient patients, though the rate of relapse is high. Rituximab is an effective and safe treatment of cytopenia associated with immunodeficiency. Although the initial response rate is 85%, there are factors that can limit its usage and decrease its efficacy, including high rate of relapse, repeated injections and severe skin infection that may occur in some cases [2, 4]. Other therapeutic choices, that have only been used in clinical trials, consist of thrombopoietin receptors agonist, bortezomib, belimumab, tocilizumab, epratuzumab and anti-APRIL antibody [4]. Splenectomy is still an option widely accepted by physicians, especially in intractable cases. The major side effect of splenectomy is post-operative infection [8]. Bone marrow transplantation may be a suitable solution for some cases. Allogenic bone marrow transplant has the highest rate of success.

Cyclosporine is an immunomodulatory drug inhibiting the immune system by affecting T-cells. It inhibits synthesis of interleukin 2, interleukin 3, interleukin

4 and interferon gamma. By contrast, cyclosporine spares the synthesis of granulocyte-macrophage colony-stimulating factors in T-cells. Thus, cyclosporine modulates the immune system by inhibiting T-cell cytokine production [9]. The common side effects of cyclosporine include headache, dizziness, hypertension, hyperlipidemia, neuropathy and nephropathy. Cyclosporine has been used successfully in controlling thrombocytopenia in patients with the antibody inhibitor of ADAMTS13. Cyclosporine also prolonged transfusion-free survival of patients with non-severe aplastic anemia, who are otherwise at a high risk of progression to transfusion-dependent aplastic anemia [10]. Despite several successful uses of cyclosporine to control cytopenia in different diseases, it has rarely been used to control cytopenia in CID cases. This case presents managing of CID-associated cytopenia with cyclosporine, whose symptoms of ITP did not respond to empirical therapies. Larger and more extended studies are needed to reveal the benefits and side effects of cyclosporine in immunodeficient patients with cytopenia.

ACKNOWLEDGEMENTS

The authors would like to thank all the individuals who took part in the study.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None.

ETHICAL APPROVAL

This article does not contain any research studies with human participants animals performed by any of the authors.

CONSENT

Informed consent was obtained from the patient's legal guardian (his mother) for publication of this case report and accompanying images. A copy of the written consent is available for review from the editor-in-chief of this journal on request.

GUARANTOR

First author is Dr Narges Bazgir accepts full responsibility for the work and/or the conduct of the study; he had access to the data and controlled the decision to publish.

REFERENCES

1. McCusker C, Upton J, Warrington R. Primary immunodeficiency. *Allergy Asthma Clin Immunol* 2018;**14**:1–12.
2. Kim J, Thrasher AJ, Jones AM, Davies EG, Cale CM. Rituximab for the treatment of autoimmune cytopenias in children with immune deficiency. *Br J Haematol* 2007;**138**:94–6.
3. Walter JE, Ayala IA, Milojevic D. Autoimmunity as a continuum in primary immunodeficiency. *Curr Opin Pediatr* 2019;**31**:851–62.
4. Seidel MG. Autoimmune and other cytopenias in primary immunodeficiencies: pathomechanisms, novel differential diagnoses, and treatment. *Blood* 2014;**124**:2337–44.
5. Abraham RS, Aubert G. Flow cytometry, a versatile tool for diagnosis and monitoring of primary immunodeficiencies. *Clin Vaccine Immunol* 2016;**23**:254–71.
6. Leiding JW, Forbes LR. Mechanism-based precision therapy for the treatment of primary immunodeficiency and primary immunodysregulatory diseases. *J Allergy Clin Immunol Pract* 2019;**7**:761–73.
7. Ghosh S, Seidel MG. Current challenges in immune and other acquired cytopenias of childhood. *Front Pediatr* 2016;**4**:3.
8. Mormile I, Punziano A, Riolo CA, Granata F, Williams M, de Paulis A *et al.* Common variable immunodeficiency and autoimmune diseases: a retrospective study of 95 adult patients in a single tertiary care center. *Front Immunol* 2021;**12**:2608.
9. Russell R, Graveley R, Coxon F, Skjodt H, Pozo ED, Elford P *et al.* Cyclosporin A. Mode of action and effects on bone and joint tissues. *Scand J Rheumatol* 1992;**21**:9–18.
10. Matsuda K, Koya J, Arai S, Nakazaki K, Nakamura F, Kurokawa M. Cyclosporine therapy in patients with transfusion-independent non-severe aplastic anemia: a retrospective analysis. *Intern Med* 2019;**58**:355–60.