An Infant with a Severe Combined Immunodeficiency Caused by Zeta Chain-Associated Protein 70 (ZAP-70) Deficiency

Mohamed Al-Shaikh, MBBs, CABP, Fellowship Allergy/Immunology* Abdulla Ali Isa, MBBs, CABP (Part-I)**
Maryam Fuad Ali, MD** Hasan M. Isa, MBBCh, CABP***

Zeta Chain-Associated Protein Kinase 70 (ZAP-70) is a protein kinase involved in the T-cell receptor (TCR) signaling; therefore, it plays a significant role in T-cell functioning. ZAP-70 related severe combined immune deficiency (SCID) is a rare autosomal recessive disorder. Various clinical presentations of the condition were described in the literature; it was suggested that this clinical heterogeneity may delay the diagnosis.

A ten-month-old infant presented with fever and cough. He was admitted to the PICU. Investigations revealed a tracheal aspirate positive for candida. This case is the first case of ZAP-70 related SCID to be reported in Bahrain.

Bahrain Med Bull 2020; 42 (1): 61 - 63

Numerous genetic mutations may interfere with humoral and cell-mediated immunity[1]. Severe combined immunodeficiency (SCID) is a heterogeneous group of genetic disorders involving defects in T and B-lymphocytes[2]. One of the mutations causing SCID is autosomal recessive mutation in the Zeta Chain-Associated Protein Kinase 70 (ZAP-70) gene[3]. ZAP-70 is a protein tyrosine kinase signaling molecule linked with T-cell receptor (TCR) complex in T-lymphocytes, hence, plays a vital role in T-lymphocytes proliferation and differentiation[4].

Deficiency in ZAP-70 results in a selective absence of CD8 T-lymphocytes in the peripheral blood[4]. CD4 T-lymphocytes count may be normal or elevated, yet, fail to respond to TCR-mediated stimuli[5]. ZAP-70 deficiency is a rare SCID with only a few cases reported in the world[3].

The aim of this report is to present the first case of ZAP-70-related SCID in the Kingdom of Bahrain, successfully treated by hematopoietic stem cell transplantation.

THE CASE

A ten-month-old Bahraini infant born at full-term via normal spontaneous vaginal delivery was referred to our institution from Bahrain Defence Force (BDF) Hospital. The patient's family is originally from Yemen. He is a product of a non-consanguinous marriage and his parents were healthy. He had three older brothers; all had similar presentations during infancy and died at 6, 7 and 8 months of age, respectively. The duration of the pregnancy was uneventful with no history of maternal infections, perinatal complications or neonatal intensive care admission. The patient was in good health until the age of 10 months, when he presented to BDF with a 3-day history of fever, cough and difficulty breathing. He was febrile with a temperature of 39C◦, tachypneic with a respiratory rate of 80 breaths per minute and hypoxemic with oxygen saturation reaching 65% on room air. Five liters of oxygen via facemask was given and his oxygen saturation rose to 98%. He had chest retractions and a tracheal tug. Auscultation revealed bilateral coarse inspiratory crepitations. Venous blood gas revealed pH of 7.36, pCO2 33, pO2 39.6 and HCO3 19. Laboratory results at BDF hospital are shown in tables 1-4.

Table 1: Laboratory Results of the Child at BDF Hospital

Parameters	Result	Unit	Reference Ranges
White blood cells count	8.3	$x10^9$/L	3.6-9.6
Hemoglobin	11.3	g/dL	12-14.5
Platelets	534	$x10^9$/L	150-400
Neutrophils	59	%	42.2-75.2
Lymphocytes	34	%	20.5-55.1
Sodium	137	mmol/L	132-146
Potassium	4.5	mmol/L	3.5-5.5
Urea	2.8	mmol/L	3.2-8.2
Creatinine	14	Micromole/L	27-62
Calcium	2.6	mmol/L	2.25-2.75
Magnesium	0.8	mmol/L	0.74-1.0
C-reactive protein	14	mg/L	0.00-7.48
Lactate dehydrogenase	532	IU/L	120-220
Blood culture	Sterile		
Tracheal aspirate	Positive for candida tropicalis		
Respiratory panel	Positive for adenovirus		

* Consultant Pediatric Immunologist
Department of Pediatrics
Senior Lecturer, Royal College of Surgeons in Ireland - Medical University Bahrain
** Resident
Department of Pediatrics
*** Consultant Pediatric Gastroenterology
Department of Pediatrics
Salmaniya Medical Complex
Assistant Professor, Arabian Gulf University
Kingdom of Bahrain
E-mail: alshaikh588@hotmail.com, halfaraj@hotmail.com, abdullaali10@live.com, mfa11241@RCSI.com

Table 2: Complete Blood Count at the Immunology Clinic

Parameters	Result	Unit	Reference Ranges
White blood cells count	7.42	$x10^9$/L	3.6-9.6
Hemoglobin	11.3	g/dL	12-14.5
Hematocrit	36.5	%	33-45
Mean cell volume	81.6	fL	80-97
Mean cell hemoglobin	25.3	Pg	27-33
Red cell distribution width	17.6	fL	11.6-13.7
Platelets	478	$x10^9$/L	150-400
Neutrophils	39.3	%	42.2-75.2
Lymphocytes	44.8	%	20.5-55.1
Monocytes	12.6	%	1.7-9.3
Eosinophils	1.7	%	1.0-4.0
Basophils	1.3	%	<2.0
Nucleated RBC	0	%	<0

RBC= red blood cells.

Table 3: Lymphocyte Subsets at the Immunology Clinic

Lymphocyte subsets		12/03/2018	25/04/2018
Natural killer cells	CD56 absolute count	189 cells/µL	898.0 cells/µL
	CD56 percent	6.3%	18%
Total T-cells	CD3 absolute count	763 cells/µL	1931.0 cells/µL
	CD3 percent	25%	58%
Helper T-cells	CD4 absolute count	Low	1848 cells/µL
	CD4 percent	24%	56%
Cytotoxic T-cells	CD8 absolute count	Low	66 cells/µL
	CD8 percent	0.2%	2%
	CD4:CD8 ratio	123.5	28
B-cells	CD19 absolute count	1976	1026 cells/µL
	CD 19 percent	56.6%	21.6%

Table 4: Immunoglobulin and Complement Proteins Levels at the Immunology Clinic

Immunoglobulin and complements	12/03/2018	25/04/2018
IgG1 subclasses	4.89 g/L	-
IgG2 subclasses	0.185 g/L	-
IgG3 subclasses	-	-
IgG4 subclasses	0.00462 g/L	-
Immunoglobulin G	5.54 g/L	4.44 g/L
Immunoglobulin A	-	1.49 g/L
Immunoglobulin M	-	0.729 g/L
Immunoglobulin E	-	Pending
C3 level	-	158 mg/dL
C4 level	-	46.6 mg/dL

IgG= immunoglobulin, C3= complement 3, C4= complement 4.

The patient remained tachypneic and not maintaining oxygen saturation with oxygen supplemented via nasal cannula. Therefore, he was electively intubated and transferred to the pediatric intensive care unit (PICU). In the PICU, he was initially kept on continuous mandatory ventilation (CMV), but he was de-saturating, thus, changed to high-frequency oscillatory ventilation (HFOV). He remained on mechanical ventilation for 11 days, after which, he was extubated and kept on nasal cannula; he was stable thereafter. Medications given during hospital admission included antimicrobials (meropenem, vancomycin, trimethoprim/sulfamethoxazole and fluconazole), salbutamol, ipratropium bromide, adrenaline, methylprednisolone, one dose of surfactant, amino acids and omeprazole. The patient was discharged in a stable condition.

In the immunology clinic, the child was vitally stable and afebrile. He was a well-thriving infant with a weight of 8.2 kilograms and height of 80 centimeters, no dysmorphic features, no hair color changes and started dentition. The tonsils were congested and enlarged and the left ear tympanic membrane was congested. Respiratory system examination revealed the presence of crepitations bilaterally; otherwise, he had an equal bilateral air entry on chest auscultation. The central nervous system, cardiovascular system, ear, nose and throat, musculoskeletal, eyes and skin examinations were unremarkable. Chest x-ray showed the presence of thymus. The patient was sent to Turkey for hematopoietic stem cell transplantation from a matched related donor (the mother). One year after the hematopoietic stem cell transplantation, the patient is doing well and healthy in terms of growth and development.

DISCUSSION

ZAP-70 deficiency is a rare form of SCID with an autosomal recessive mode of inheritance[3]. ZAP-70 related SCID was first described in 1994. Nevertheless, only more than 50 cases have been described in the literature to date[5].

According to the literature, the age at which patients with ZAP-70 deficiency present is variable[3]. The majority of cases present before 12 months of age and children often do not survive past their second year of life without hematopoietic stem cell transplantation[9]. Similarly, our patient was apparently well until the age of 10 months.

It was previously emphasized that the clinical heterogeneity of ZAP-70 deficiency is one factor that impairs the diagnosis[6]. Previously reported studies showed variable presentations of ZAP-70. A two-month old infant who presented with eczematous skin lesions, a seven-month-old infant who presented with Kawasaki disease-like features, and an eleven-month-old infant who presented with diffuse large B-cell lymphoma were reported[6-8].

Clinically, ZAP-70 SCID differs from most SCID in that patients with ZAP-70 deficiency often have palpable lymph nodes and normal thymus[10].

In our case report, the patient presented with a lower respiratory tract infection and a positive tracheal aspirate for candida and laboratory findings of only 66 cells/µL absolute CD8 cell count and abundance of CD4 cells (an absolute count of 1848 cells/µL).

The diagnosis of this patient was based on clinical presentation and laboratory findings with the absence of CD8 cytotoxic T-cells in the flow cytometry. No genetic test has been done for the patient at the time of this report, which is considered a limitation.

CONCLUSION

This is the first reported case in Bahrain of an infant with severe combined immunodeficiency caused by Zeta Chain-Associated Protein 70 (ZAP-70) Deficiency. He was treated successfully with hematopoietic stem cell transplantation.

Author Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None.

Competing Interest: None.

Sponsorship: None.

Acceptance Date: 31 August 2019.

Ethical Approval: Approved by the Secondary Care Medical Research Subcommittee, Salmaniya Medical Complex, Ministry of Health, Bahrain. Conducted in accordance with the principles of Helsinki Declaration.

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63