LPS-Responsive Beige-Like Anchor Gene Mutation Associated With Possible Bronchiolitis Obliterans Organizing Pneumonia Associated With Hypogammaglobulinemia and Normal IgM Phenotype and Low Number of B Cells

Sima Shokri[1], Mohammad Nabavi[1], Tatjana Hirschmugl[2], Asghar Aghamohammadi[3], Saba Arshi[1], Mohamad Hassan Bemanian[1], Morteza Fallahpour[1], Rasool Molatefi[1], Mahsa Rekabi[1], Narges Eslami[1], Javad Ahmadian[1], Kian Darabi[1], Gholam Reza Sedighi[1], Maryam Monajemzadeh[5], Mohammadreza Modaresi[5,6], Nima Parvaneh[3], Kaan Boztug[2,7], and Nima Rezaei[3,4,8]

[1] Department of Allergy and Clinical Immunology, Rasool-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

[2] CeMM Research Center for Molecular Medicine, Austrian Academy of Sciences, Vienna, Austria

[3] Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

[4] Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[5] Pediatrics Center for Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

[6] Pediatric Respiratory Diseases Education and Research Network (PRDERN), Universal Scientific Education and Research Network (USERN), Tehran, Iran

[7] Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria

[8] Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Boston, MA, USA

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Abstract- LPS-Responsive Beige-like Anchor (LRBA) deficiency is a disease which has recently been described in a group of patients with common variable immunodeficiency (CVID) in association with autoimmunity and/or inflammatory bowel disease (IBD)-like phenotype. We here describe a 10-year-old boy who experienced recurrent infections, mainly in the respiratory system, associated with thrombocytopenia and anemia. Immunological workup showed low numbers of B cells and low IgG, but normal IgM levels. In spite of therapeutic doses of antibiotics, antivirals, and antifungal agents, in addition to immunoglobulin replacement therapy, he developed disseminated involvement of both lungs with peripheral nodules; transbronchial lung biopsy revealed possible bronchiolitis obliterans organizing pneumonia (BOOP). Combined homozygosity mapping and exome sequencing identified a homozygous *LRBA* mutation in this patient (p.Asp248Glufs*2). Such clinical and immunological findings have not been described to date and illustrate the broad and variable clinical phenotype of human LRBA deficiency.

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Introduction

Lipopolysaccharide responsive beige-like anchor (LRBA) is an essential gene for the normal function of the immune system. Mutations of the *LRBA* gene have recently been reported in common variable immunodeficiency (CVID) and autoimmunity (1,2). It seems that inflammatory bowel disease (IBD)-like phenotype in addition to hypogammaglobulinemia and autoimmunity are the main features of patients with LRBA deficiency (1-3).

Interstitial lung diseases (ILD) represent one of the most important late-onset complications of immunodeficient patients, which are rarely seen in

Corresponding Author: N. Rezaei
Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 66929234, Fax: +98 21 66929235, E-mail address: rezaei_nima@tums.ac.ir

children (4). Bronchiolitis obliterans organizing pneumonia (BOOP) is a clinicopathologic syndrome, clinically apparent by sub-acute or chronic dry cough and shortness of breath. BOOP is characterized histopathologically by the presence of granulation tissue in the bronchiolar lumen, alveolar ducts, and some alveoli, associated with variable degrees of interstitial and airspace infiltration by mononuclear cells and foamy macrophages (5).

Materials and Methods

Herein, a 10-year-old Persian boy is presented who was referred to our center with recurrent infections and autoimmunity. His parents are cousins and healthy. He has a 5-year-old healthy sister, and there is no history of sibling death in the family. His uncle has died because of hematologic malignancy. He was 2 when he came with a history of an episode of severe upper respiratory infection and gastroenteritis leading to hospitalization at 2 years of age. Severe disseminated varicella infection occurred 8 months later and soon afterward he developed thrombocytopenia and splenomegaly and had received intravenous immunoglobulin (IVIG) therapy with an initial diagnosis of Immune Thrombocytopenic Purpura (ITP) after bone marrow smears did not show any pathology. He experienced chronic and recurrent oral thrush and multiple episodes of acute immune hemolytic anemia with warm autoantibodies, positive coombs test, while the repeat bone marrow aspiration at four years of age was normal. Frequent otitis media and mastoiditis led to mastoidectomy of the patient, while unilateral sensory-neural hearing loss and facial nerve palsy remained as a consequence of contagious infection of the ear or another autoimmune process.

When he was 7-year-old, he developed a brain abscess, but no microorganism was detected. Severe respiratory involvement included a productive cough, exertional dyspnea, and shortness of breath and cyanosis with the progressive course and became obvious after the age of 8 years.

Results

Immunological workup was compatible with an immunodeficiency with decreased IgG and IgA, but normal IgM phenotype, and a low number of B cells (Table 1).

Table 1. Immunological workup of the patient with LRBA deficiency

Variable	Amount	Unit	Normal range
IgG	47	Mg/dl	386-1470
IgA	45	Mg/dl	29-256
IgM	193	Mg/dl	37-224
IgE	2.7	IU/ml	22.7-317
WBC	5800	/Microlitre	4000-12500
PMN	3712	/Microlitre	--
LYM	1682	/Microlitre	--
MONO	348	/Microlitre	--
EO	58	/Microlitre	--
Absolute lymphocyte count	1682	/Microlitre	1400-3700
Absolute CD3+T cells	1429	/Microlitre	1200-2600
Absolute CD4+T cells	555	/Microlitre	650-1500
Absolute CD8+T cells	841	/Microlitre	370-1100
Absolute CD16+NK cells	176	/Microlitre	100-480
Absolute CD56+NK cells	185	/Microlitre	100-480
Absolute CD19+B cells	134	/Microlitre	270-860
Absolute CD20+Bcells	117	/Microlitre	270-860
White blood cells in smear	20-22	/HPF	>25/HPF
Epithelial cells in smear	1-2	/HPF	<10/HPF
Bacterial culture	>100000	CFU/mL	Negative
Cytomegalovirus genome	positive	-	Negative
Pneumocystis genome	positive	-	Negative
Mycobacterium tuberculosis genome	negative	-	Negative

Serologic studies for EBV and CMV was negative at that time (IgG and IgM). Accordingly, monthly IVIG substitution was commenced. Despite regular IVIG treatment, the pulmonary condition worsened and computed tomography (CT) scan revealed diffuse nodular involvement in peripheral areas of both lungs. Bronchoalveolar lavage showed concomitant colonization with *Pseudomonas aeruginosin*, *Pneumocystis jirovecii* and CMV (positive on PCR). Despite therapeutic doses of antibiotics, antivirals, and antifungal agents, the respiratory signs and symptoms progressed, and CT scan revealed the disseminated involvement of both lungs with peripheral nodules (Figure 1).

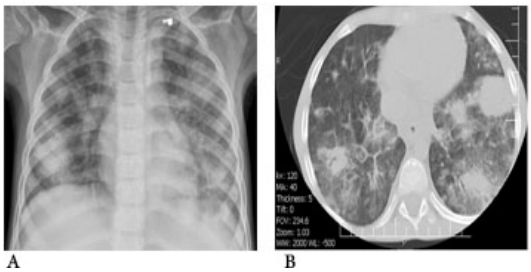

Figure 1. Chest X-ray (A) and chest CT scan (B) of the patient with LRBA deficiency and possible BOOP.

Transbronchial lung biopsy was performed and showed lung tissue infiltration by severe inflammatory cells including lymphocytes, PMN leukocytes, few plasma cells and numerous macrophages, PAS and Ziehl-Neelsen staining shows no fungal or acid fast bacilli respectively. In some area, the histology is reminiscent to beginning a phase of bronchiolitis obliterans with organizing pneumonia (BOOP), which is a form of interstitial lung disease (Figure 2).

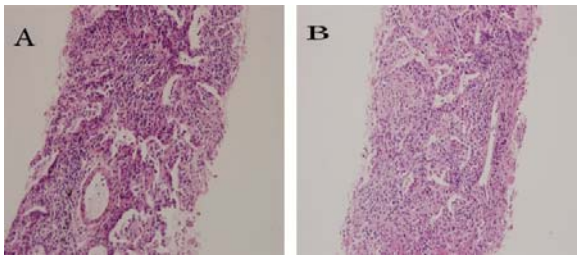

Figure 2. Histopathology of bronchiolitis obliterans with organizing pneumonia (BOOP). A. The section shows lung tissue, infiltrated by severe inflammatory cells, including lymphocytes, PMN-leukocytes, few plasma cells, and numerous macrophages. PAS and Ziehl-Neelsen staining shows no fungal elements or acid-fast bacilli, respectively. B. In some area, the histology is reminiscent to beginning a phase of BOOP.

Pulmonary symptoms improved markedly after treatment with systemic corticosteroids, but no imaging of lungs has been performed after therapy. Simultaneously, blood PCR for EBV, CMV, HSV and adenovirus were studied which were all negative.

CD40LG gene was sequenced, which was intact. Combined homozygosity mapping and exome sequencing confirmed a homozygous, severe mutation in the *LRBA* gene, leading to frameshift insertion (NM_001199282:c.743_744insAAGA:p.Asp248Glufs*2) (6). Both parents were heterozygous carriers of the mutation, in line with the known autosomal recessive mode of inheritance.

Discussion

According to previous reports, LRBA deficiency usually presents with a variety of manifestations, including hypogammaglobulinemia, accompanied by autoimmune disorders and/or IBD-like phenotype (7-10). However, this case has a low level of IgG in association with normal IgM level. Moreover, a low number of B cells resembled an autosomal or X-linked agammaglobulinemia with low B cell number. However, Next Generation Sequencing (NGS) confirmed the diagnosis of LRBA deficiency in this case. In addition, BOOP is one of the rarest pulmonary complications of primary immunodeficiency diseases (PIDs) in children, as it is usually among the late onset complications. The occurrence of such immunodeficiency phenotype due to *LRBA* mutation and occurrence of BOOP in childhood as a complication of primary immunodeficiency has not been reported yet, especially in children. Meanwhile, mutations in this gene could also lead to a variety of immunodeficiencies, ranging from an immunoglobulin deficiency to low a number of B cells.

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