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Case Report

A Novel Case of SHORT Syndrome Presenting with Very Early Onset Inflammatory Bowel Disease (VEO-IBD)

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Abstract

Herein we report a novel case of SHORT syndrome with very early onset inflammatory bowel disease (VEO-IBD). He presented with hematochezia since the first months of life for which he was diagnosed with cow milk allergy that did not respond to treatment. He underwent a colonoscopy confirming the diagnosis of ulcerative colitis (UC). His past medical history was also remarkable with delayed growth since 6 months of age and frequent hospitalizations due to recurrent fever, gastroenteritis, and anemia with no history of recurrent infectious episodes. Despite appropriate treatment for UC and partial improvement in his bowel habits and nutrition, there was no improvement in his growth status and he was found to have failure to thrive. The patient further underwent genetic test evaluation and a novel heterozygous missense mutation was detected in the *PIK3R1* gene (c.2076A>C, P. Lys692Asn) confirming the diagnosis of SHORT syndrome. He got appropriate treatment and is currently doing well, in good condition and is under regular monthly follow-up.

Keywords: Activated p110δ Syndrome; Primary Immunodeficiency Disorders; *PIK3R1*; SHORT Syndrome; Very Early Onset Inflammatory Disease

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Introduction

SHORT syndrome (standing for short stature, hyperextensibility of joints and/or hernia, ocular depression, Rieger anomaly, and teething delay) is a rare genetic disorder caused by heterozygous loss-of-function (LOF) mutations in phosphatidylinositol 3-kinase regulatory subunit 1 (*PIK3R1*) gene and is characterized by multiple congenital internal organ defects and dysmorphic features including facial gestalt (triangular face with a small chin, downturned mouth, low-set posteriorly rotated ears, promi

nent forehead, lack of facial fat, and hypoplastic nasal alae with overhanging columella), hearing loss, nephrocalcinosis, lipoatrophy and insulin resistance (1-5). In most of the cases, the affected patients are mentally normal (2). Also, they reach and pass the developmental milestones normally (2).

Phosphoinositide 3-kinases (PI3Ks), also known as phosphatidylinositol 3-kinases, are a family member of the intracellular downstream signaling transducer enzymes. They are categorized into 3 classes (6). The p110 catalytic and p85 regulatory subunits together form the heterodimer class IA PI3Kδ (6). The p85α regulatory subunit is encoded by the *PIK3R1* gene (6). PI3Kδ is mainly expressed in leukocytes and has crucial roles in several lymphocyte functions including cellular proliferation, differentiation, proper growth and survival as well as intracellular trafficking (7, 8). These functions are modulated through the PIK3/ protein kinase B (AKT)/ mammalian target of rapamycin (mTOR) signaling pathway (7, 8). Downstream of the antigen receptor (either B cell receptor, T cell receptor or Toll-like receptor), phosphatidylinositol 4,5-biphosphate (PIP2) is phosphorylated and converted to phosphatidylinositol 3,4,5-triphosphate (PIP3). Then, PIP3 activates AKT, enhancing the mTOR signaling pathway (9). Mutations of *PIK3R1* gene are reported to be associated with two different conditions, the aforementioned SHORT syndrome and a rare primary immunodeficiency disorder named activated PI3K-delta syndrome 2 (APDS2) (10).

Herein, we aim to report a novel case of SHORT syndrome presenting with very early onset inflammatory bowel disease (VEO-IBD). He presented with hematochezia since infancy and was being treated based on the diagnosis of food allergy. His symptoms did not relieve in spite of appropriate treatment and normal laboratory data and he was not growing at the normal rate for his age. Thus, he underwent genetic testing and finally was diagnosed with SHORT syndrome.

Case presentation

The patient is a 4-year-old male born to non-consanguineous healthy parents. The patient was born through a cesarean delivery at term. His birth weight, height, and head circumference were in the 15th percentile for weight and height and under the 5th percentile for head circumference. His weight was at the 85th percentile line on the growth chart till 6th month of age but from then on he started to experience delayed growth. Since his first months of life, he had blood in his stool for which a diagnosis of cow milk allergy was made when he was 13 months old. Based on this diagnosis, the infant was switched to a hypoallergenic formula, and his mother was placed on a dairy-free diet. Despite the appropriateness of the treatment for food allergy, the patient's hematochezia continued. He also suffered from recurrent abdominal pain and restlessness. A precise assessment of his past medical history revealed frequent hospitalizations due to recurrent fever, gastroenteritis, and anemia with no history of recurrent infectious episodes. The patient was referred for further investigation. Laboratory analysis revealed anemia along with hypergammaglobulinemia **(Table 1).** The patient underwent a colonoscopy and a diagnosis of ulcerative colitis (UC) was made for him. The patient was treated with prednisolone 2.5 mg daily, and mesalazine 500 mg daily along with diet and nutrition alterations. Subsequently, his medical condition was partially improved including cessation of diarrhea and improved nutrition; however, there was no improvement in his growth status.

At 4 years of age, a short stature, small chin, and teething delay were detected on physical examination indicative of the presence of failure to thrive (FTT) **(Figure 1)**. Due to the underlying FTT, the patient became a candidate for genetic evaluation exome sequencing was performed for the patient and a novel heterozygous missense mutation, c.2076A>C (NM_181523.3), was detected in the *PIK3R1* gene leading to amino acid change P. Lys692Asn. Based on the American College of Medical Genetics and Genomics (ACMG) for variant classification, this mutation is classified as a variant of unknown significance (VUS). Finally, the child was diagnosed with SHORT syndrome and got appropriate treatment. He is currently doing well and in good condition and is under regular monthly follow-up.

Discussion

In the current study, we have reported a novel case of SHORT syndrome with VEO-IBD who was diagnosed with and treated for cow milk allergy during infant stage and UC during toddler

Table 1. Laboratory data of the patient at time of his gastrointestinal manifestations and growth retardation.

Parameters	Values
WBC, cells/µl	9880
Lymphocytes, cells/µl	4360
$CD3^+$, cells/µl	1383
$CD4^+$, cells/µl	745
$CD8^+$, cells/µl	399
$CD19^+$, cells/µl	239
$CD56^+$, cells/µl	585
Neutrophils, cells/µl	3880
Monocytes, cells/µl	1530
Eosinophils, cells/µl	110
Hb, g/dl	**8.7↓**
MCV, fL	70.4
Platelets, cells/µl	**625000↑**
Fecal calprotectin Ag, mg/kg	**836.1↑**
ESR 1st hour	**62↑**
CRP	negative
IgG, mg/dl	**1815↑**
IgM, mg/dl	156
IgA, mg/dl	**241↑**
IgE, IU/ml	**47.4↑**
Anti-TTG Ab	0.1
Calcium, mg/dl	9.4
Phosphorus, mg/dl	5.9
Protein total, g/dl	7.2
Albumin, g/dl	4.7

WBC, white blood cells; µl, microliter; Hb, hemoglobin; dl, deciliter; MCV, mean corpuscular volume; fL, femtoliter; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; mg, milligram; TTG, tissue transglutaminase.

stage. Despite partial improvement in his bowel habits and nutrition, there was no improvement in his growth status and he was found to suffer from FTT. This led us to further study the patient via genetic test evaluation in which a novel heterozygous missense mutation was detected in the *PIK3R1* gene (c.2076A>C, P. Lys692Asn), and the diagnosis of SHORT syndrome was made for which he got appropriate treatment and is currently in good condition.

VEO-IBD is defined as clinical manifestations of IBD and/or receiving the diagnosis before 6 years of age (11, 12). VEO-IBD has some distinct characteristics like a higher likelihood of an underlying monogenic etiology or primary immunodeficiency disorder (PID) as well as resistance for conventional therapy for IBD in comparison to IBD diagnosed in older children (13). The identified etiologies to date can be divided into 6 groups: including T and B cell defects, general immune dysregulation, phagocytic defects, autoinflammatory disorders, epithelial barrier dysfunction and other conditions (14, 15). A large proportion of the currently identified monogenic etiologies of VEO-IBD reflect underlying PIDs highlighting the importance of considering PIDs in any patient with VEO-IBD and performing a thorough and detailed immune workup in patients with VEO-IBD to identify possible underlying immunodeficiencies even in the absence of chronic, recurrent, or atypical infections (16). In case of the absence of clear clinical suspicion for an underlying monogenic etiology or unrevealing specialized directed testing, a more expansive evaluation using either targeted gene panels for VEO-IBD or next-generation sequencing is required (16). In our case, treatment for cow's milk protein intolerance did not show a positive response. Also, treatment for UC showed partial improvement in nutrition and bowel habits without any changes in the growth status of the patient.

The patient did not have recurrent infectious episodes in his past medical history and his im-

Figure 1. Image of the patient at 4 years of age. A. Facial abnormalities including triangular face with a small chin and downturned mouth as well as irregular teeth. B. Low-set ears. C. Short stature.

munological pattern was not compatible with PID, thus we decided to perform a genetic study to evaluate the patient's condition and detected a heterozygous missense mutation in the *PIK3R1* gene and confirmed the diagnosis of the SHORT syndrome.

Mutations in *PIK3R1* are reported to be associated with 3 inherited human diseases (17): 1. SHORT syndrome characterized by short stature, hyperextensible joints, Rieger anomaly of the eye, teething delay, lipoatrophy, and often insulin resistance and caused by heterozygous mutations in *PIK3R1* with autosomal dominant inheritance pattern (3, 18); 2. APDS2 is characterized by recurrent infections of the respiratory tract, lymphoproliferation, and malignancy and caused by loss of function mutations in *PIK3R1* with autosomal dominant inheritance pattern (19, 20); and 3. Agammaglobulinemia is characterized by recurrent infections and absent B cells and caused by homozygous mutations in *PIK3R1* with autosomal recessive inheritance pattern (21, 22). This highlights the importance of a multidisciplinary approach and simultaneous assessment of clinical manifestations and immunological findings along with genetic study to distinguish between various conditions and phenotypes caused by mutations in a distinct gene to initiate the proper treatment for the affected patients.

PI3K-AKT-mTOR pathway has pivotal roles in cellular proliferation and growth (23). Dominant mutations in *PIK3R1* are associated with impaired cell division and growth retardation by the mechanism of suppressed signal transduction in the PI3K-AKT-mTOR pathway and downregulation of it (5). Other cardinal features of the SHORT syndrome include lipoatrophy, insulin resistance, nephrocalcinosis, and disordered calcium metabolism, which should be monitored regularly to be diagnosed and managed timely before the occurrence of irreversible sequels such as diabetes mellitus-associated complications, renal stones, and kidney injury (24-27).

Conclusion

In the current study, we have reported a novel case of SHORT syndrome with VEO-IBD who was diagnosed with and treated for UC in toddler age as the underlying cause for his symptoms. However, the patient continued to have delayed growth and FTT despite appropriate treatment for UC and partial improvement in his nutrition. This led us to further evaluate the patient and make the diagnosis of SHORT syndrome due to an underlying mutation in the *PIK3R1* gene for which he received appropriate treatment and is currently in good condition. A review of this case shows that in addition to paying attention to the pathology of the disease, sometimes features of appearance could also be a guide for diagnosing the disease, which should be considered.

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Conflict of interest

The authors declare no conflict of interest.

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