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Case Report

Case Report: Activating PIK3CD Mutation in a Patient with Refractory Ascites

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Abstract

Background: Activated phosphoinositide 3-kinase delta syndrome (APDS) is a recently described combined immunodeficiency condition resulting from gain-of-function mutations in PIK3CD, which encodes the catalytic subunit of phosphoinositide 3-kinase D (PI3Kd). Mutations in PIK3CD cause primary immunodeficiency with a spectrum of clinical manifestations characterized by recurrent respiratory tract infections, susceptibility to uncontrolled viral infections, impaired vaccine response, autoimmunity, hepatosplenomegaly, and an increased incidence of B-cell lymphoproliferation and lymphoma. Diagnosis of these deficiencies is crucial for their management. In recent years, targeted treatment with selective PI3Kd inhibitors has had a substantial effect on controlling the symptoms of these diseases. **Case Presentation:** Herein, we report a case of a patient with genetically confirmed PIK3CD mutation who initially presented with generalized lymphadenopathy. Hepatosplenomegaly complicated by immune-mediated anemia and thrombocytopenia resolved after a splenectomy. Over the next few months, the patient developed idiopathic, severe, and refractory chronic ascites requiring repeated diagnostic and therapeutic paracentesis. We hypothesized that autoimmune ascites, after exclusion of common and rare causes of ascites, especially the PIK3CD mutation, is a risk factor for autoimmune complications. The patient responded well to the corticosteroid therapy. **Conclusion**: PIK3CD mutation is a rare primary immune disease associated with immune dysregulation, immunodeficiency, and malignancy. Autoimmune ascites is an extremely rarely reported complication that needs to be considered after ruling out other known causes.

Keywords: Activated PI3Kδ Syndrome; PIK3CD; Genetic variant; Sirolimus

Introduction

Primary immunodeficiencies are inherited disorders of the immune system that include approximately 500 single-gene inborn errors of immunity [1,2]. Genetic defects in the immune system lead to an increased susceptibility to recurrent, severe, or unusual infections. Recently, germline heterozygous gain-of-function (GOF) mutations in PIK3CD, encoding catalytic p110δ, have been shown to cause a primary immunodeficiency. Mutations in this gene can result in lymphadenopathy and combined immunodeficiency and have been reported to induce immunodeficiency in different ways [3]. Activated phosphoinositide 3-kinase δ syndrome (APDS)

is a rare, autosomal dominant primary immunodeficiency caused by GOF mutation in PIK3CD or PIK3R1 genes. Overactivation of this kinase leads to the activation of mTOR, promotion of cell growth and protein synthesis, and inhibition of apoptosis, leading to autoimmunity, lymphoproliferation, and recurrent infections. Paradoxically, both loss-of-function and gain-of-function mutations of these genes lead to immunosuppression through different mechanisms [4,5]. The biochemical and clinical symptoms of patients with APDS1 (PIK3CD mutations) and APDS2 (PIK3R1 mutations) are similar [6,7]. (Tables 1)

Laboratory investigations	During admission and follow-up (before splenectomy)			After splenectomy	Recent Lab Values	Reference
White blood cell	14.34	1.84	3.74	27.78	23.9	4–12
Hemoglobin (g/dL)	7.5 g/L	7.4	9.1	11	9.98	12.9–15.5
Neutrophils	5.3	0.5	3	21.2	16.6	
Platelets	98	29	64	848	596	150–350
Retic count	7.76	5.75	7.69			
PT second	2.3	11.6	13.3	5.54	14.2	12.3–14.7
INR	1	1.1	1		1.1	0.8–1.2
PTT second	38	30	40		34.1	26–40
ESR	120	120	120	120	130	0–30 mm/h
CRP (mg/L)	221	78	9.37	75.36	10	<10
ALT	12	14	4.6	2.3	43	0–41
AST	20	54	13.1	18.1	42	0–40
ALP	130	107	92	129	170	<115
LDH	404	315	100		273	<248
Amylase	20				11	
Total protein	(77.3 g/dl)					
Bilirubin total	(6 µmol\L)					
Immunological work up						
IgA (g/L)	<0.3 g/dl	0.21	0.34		<0.5	0.76–3.9
IgG (g/L)	1.1 g/dl	2.5 g/dl	5.3 g/dl		6.78 g/dl	7.0–16.0
IgM (g/L)	41.6 g/dl	18.81 g /dl	10 g/dl		7.34 g/dl	0.45–2.30
IgE	6.3					
CD3 Absolute count	3517					2000–6900
CD19 Absolute count	86					700–2500
CD16+CD56 Absolute count	619					100–1000
CD3+CD4 Absolute count	581					14005100
CD3+CD8 Absolute count	2635					600–2100
Sodium	141	139	138			
Potassium	4.6	4.8	4.87			

Phosphorus	1.58	1.04	1.45			
Magnesium	0.94	0.78	1.02			
Urea	1.03	3.6	1.8			
Creatinine	18.7	18.8	24			
Albumin	29.87	31.3	32			
Ferritin	130.2					
Ammonia	63.1					
Anti SSA(RO)	Normal					
Antibody 1.7 units						

Table 1: Laboratory Investigation.

Case Presentation

A patient was admitted with septic arthritis when he was 12 months old and received a full course of antibiotics. Two months later, he had a similar episode. At 25 months, he was admitted with severe pneumonia and pleural effusion to the PICU, where he remained for a few days, and then moved to the general ward. At 29 months of age, he was admitted for bronchopneumonia.

At the age of 3 years, he was referred to our hospital, King Saud Medical City, with progressive abdominal distension, hepatosplenomegaly, and cytopenia. He thoroughly examined and common infectious, oncological, and metabolic causes were excluded. The basic immune workup was abnormal and showed high IgM and low IgG and IgA levels. Gene testing confirmed a heterozygous variant of the PIK3CD mutation. Therefore, regular intravenous immunoglobulin, prophylactic trimethoprim-sulfamethoxazole, and a pre-stem cell transplantation workup was initiated. He continued to have recurrent severe anemia and thrombocytopenia that required irradiated PRBC and platelet transfusion and did not respond well to corticosteroid and immunosuppressive therapy. Therefore, the patient underwent a splenectomy, which resulted in a substantial improvement in his blood profile. Rapamycin (sirolimus) was initiated, and the dose was adjusted based on serum drug levels.

However.with absence of peritonitis, ascetic fluids were transudate and serum ascetic albumin gradient (SAAG) more than 1.1g/dL marked inflammatory cells with lymphocyte predominant. Ascetic fluids repeatedly were negative for acid-fast bacilli, fungal infection and malignant cells. hepatic Doppler ultrasound showed patent portal vein with normal blood flow. CT-guided liver biopsy had no evidence of liver cirrhosis. bone marrow and lymph nodes excisional biopsies were negative for malignancies, acid-fast bacilli and fungal infections .Upper endoscopy and colonoscopy did not show evidence of inflammatory bowel disease . Echocardiogram revealed normal cardiac anatomy and contractility. Spot urine for protein creatinine ratio within normal range. Serologic tests including C3 ,C4 and ANA all were normal .ascetic fluid triglyceride and amylase level repeatedly were normal.

Therefore, autoimmunity-related ascites was considered, and oral prednisolone was initiated at 2 mg/kg/d for two weeks then tapered gradually over six months. During the therapy, the patient was ascites-free for six months. However, at the end of corticosteroid tapering (0.125 mg/kg/dose) every other day, the patient experienced ascites relapse. Therefore, the initial prednisolone dose was resumed, and azathioprine was started. The patient was referred to a higher center for stem cell bone marrow transplantation.

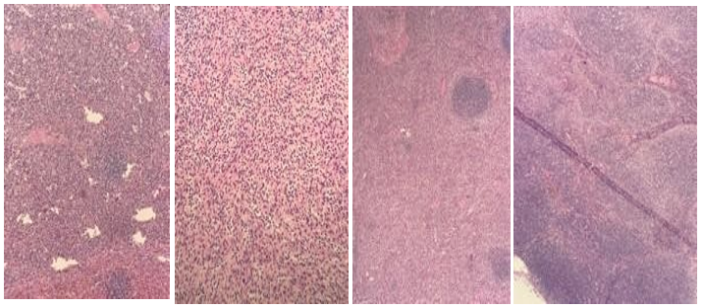

Figure 1: A, B. Part of the spleen; C. Wedge biopsy showing expanded red bulb by sinusoidal dilatation, old hemorrhage (hemosiderin laden macrophages identified), fibrosis (feature of hemolytic anemia), and no malignancy.D. Lymph node biopsy showing reactive lymphoid hyperplasia and no malignancy.

Discussion

We present an overview of the clinical course of a patient with a unique clinical presentation of refractory ascites. Here, we report a case of a heterozygous, pathogenic, variant of PIK3CD, known as Known Saudi Mutation, including deleterious variants of PIK3CD. The present case is worth reporting because of the

novelty of one of the clinical presentations of refractory ascites with undetectable causes. To the best of our knowledge, no PIK3CD mutations have been reported in patients with refractory autoimmune ascites.

In 2018, Simone et al. reported a case of 67-year-old male patients with autoimmune ascites who responded well to mycophenolate mofetil. APDS is a heterogeneous inborn error of immunity (IEI), first reported in 2013 [4]. It is caused by autosomal dominant mutations in PIK3CD (resulting in APDS1) or PIK3R1 (resulting in APDS2), which increases the activity of phosphoinositide-3-kinase delta (PI3Kd) [6]. Unfortunately, activating somatic PIK3CD mutations have been associated with variable clinical features, ranging from asymptomatic to severe immunodeficiency, causing profound complications and early death.

The most common clinical manifestation of APDS is recurrent respiratory infection. A complication of frequent respiratory tract infections is bronchiectasis [8], in addition to lymphoproliferative and autoinflammatory disease. Autoimmune presentations are features of APDS1 in up to 42% of cases [9]. Among these, were the most frequent manifestations, followed by Evans syndrome, type 1 diabetes mellitus, enteropathy, arthritis, SLE, autoimmune thyroiditis, sclerosing cholangitis, Sjogren syndrome, and autoimmune hepatitis [10,11].

Lymphoproliferation leads to lymphadenopathy and organomegaly and increases the risk of malignant lymphoma [12,13]. Some patients also experience failure to thrive, neurocognitive development, and syndromic features unrelated to immunodeficiency, especially APDS2, hyperextensibility of short stature, hyperextensibility of joints, and PIK3R1 variants [14].

Whole-genome sequencing is likely to become routine in IEI in the future. The new molecules being approved as targeted therapies will gain importance for the treatment of APDS and IEI in general [15] Genetic testing is a promising approach, and diagnosis via genetic testing is given priority over the clinical and even laboratory phenotypes and has been used successfully in diagnosing rare diseases [16].

Although our patient underwent two lymph node biopsies and a bone marrow biopsy that revealed no malignancies, he still requires long-term follow-up and lymph node biopsies in the future. The risk of malignancy increases with age. His initial presentation was pancytopenia (autoimmune anemia and thrombocytopenia), which responded well to splenectomy.

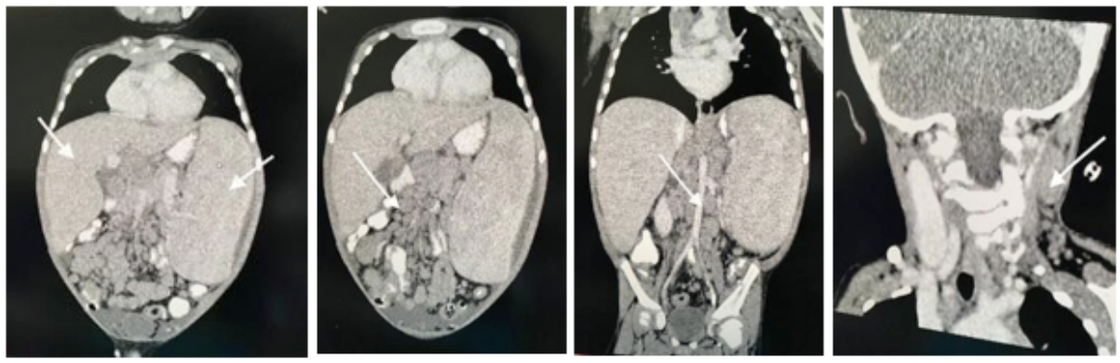

Figure 2: A. This is coronal cut showing a significantly enlarged liver and spleen. B. Abdominal CT showing multiple retroperitoneal lymph nodes. C. Abdominal CT and pelvis showing multiple mesenteric lymph node enlargement.

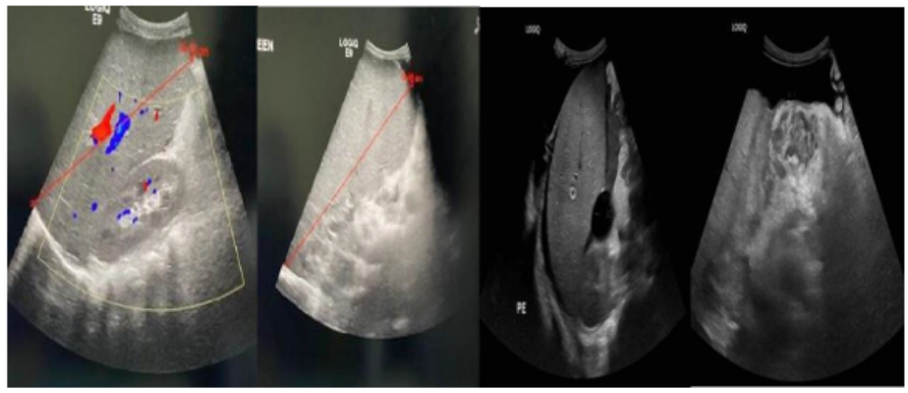

Figure 3: A. Ultrasound of abdomen showing enlarged liver with liver span of 14.03 cm. B. Ultrasound of abdomen showing enlarged spleen 19.45 cm. C. Moderate amount of free ascites fluid noted in the abdomen and pelvis. The largest amount in the left lower quadrant is unchanged compared to previous study.

Patients with APDS display autoimmune phenotypes, with almost 50% of them exhibiting autoimmune-mediated organ damage, such as thrombocytopenia [6]. An overview of this case provides new information regarding the broad spectrum of clinical manifestations of the disease by including ascites as an evolution over time. Rapamycin (sirolimus) was initially administered along with intravenous immunoglobulin and trimethoprim/sulfamethoxazole as prophylaxis during the early stages of genetic testing [17].

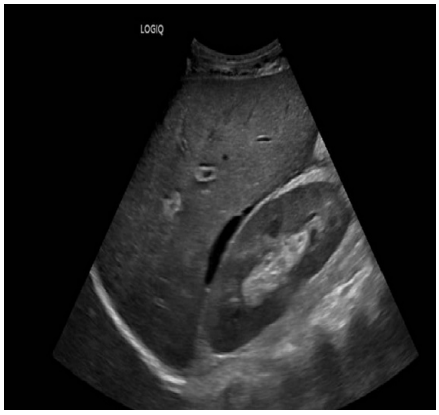

Figure 4: Overall improvement of previous intra-abdominal free ascites as a trace amount of free ascites not amenable for drainage.

The patient was transferred to the KFSH&RC for bone marrow transplantation because hematopoietic stem cell transplantation (HSCT) can be a curative approach.unfortunatley have no full matched donor. The efficacy and safety of sirolimus remain uncertain in patients with APDS; therefore, long-term follow-up is needed [18]. The recently reported PI3Kδ inhibitor, leniolisib, showed an excellent control of the lymphoproliferation and also improved the cytopenias at the end of treatment [19]. The FDA has approved it as the first-line treatment for activated PI3Kδ syndrome in adult and pediatric patients of 12 years of age [20,21]. Allogeneic HSCT is a curative option; however, it is associated with a mortality rate of approximately 20%, and it is unclear whether severe lung disease can be reversed. Additionally, it can cause graft versus-host disease [22-24].

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