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CASE REPORT

Recurrent eosinophilia with a novel homozygous ARPC1B mutation

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Abstract Cytoskeletal network dysregulation is a pivotal determinant in various immunodeficiencies and autoinflammatory conditions. This report reviews the significance of actin remodeling in disease pathogenesis, focusing on the Arp2/3 complex and its regulatory subunit actin related protein 2/3 complex subunit 1B (ARPC1B). A spectrum of cellular dysfunctions associated with ARPC1B deficiency, impacting diverse immune cell types, is elucidated. The study presents a patient featuring recurrent and persistent eosinophilia attributed to homozygous ARPC1B mutation alongside concomitant compound heterozygous cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations. We used ARPC1B antibody to stain the patient's peripheral blood lymphocytes and those of the control. The defect in the ARPC1B gene in the present patient caused absent/low expression by immunofluorescence microscopy. The intricate interplay between cytoskeletal defects and immunological manifestations underscores the complexity of disease phenotypes, warranting further exploration for targeted therapeutic strategies.

Keywords actin cytoskeleton defects; ARPC1B deficiency; hypereosinophilia; primary immunodeficiency; cystic fibrosis

Introduction

Defects in the cytoskeleton networks can lead to various immunodeficiencies and autoinflammatory diseases. So far, more than 20 monogenic disorders related to actin remodeling have been identified [1], and common gene defects affecting actin cytoskeleton and leading to eosinophilia are the *DOCK8* and *RLTPR* defects. Another protein group related to the actin cytoskeleton involves the Arp2/3 complex, which regulates actin polymerization. The Arp2/3 complex consists of seven subunits, with its two subunits, Arp2 and Arp3, being members of the actin-related protein families. The remaining five regulatory subunits are ARPC1, ARPC2, ARPC3, ARPC4, and ARPC5. Humans have two isoforms of ARPC1, namely ARPC1A and ARPC1B. ARPC1B is predominantly expressed in blood cells and is involved in actin branching. The deficiency of ARPC1B can affect various cell types, such as platelets, antigen-presenting dendritic cells, monocytes/macrophages, neutrophils, B cells, and T cells in distinct ways. For instance, in B cells, ARPC1B has a regulatory function in the cortical cytoskeleton and is a determinant factor in B cell activation. In cytotoxic T cells lacking ARPC1B, the expression of essential components for function, such as T cell receptors, CD8, and GLUT1, is decreased [2,3].

Kuijpers *et al*. described the first case of primary immunodeficiency caused by an ARPC1B mutation [4]. Homozygous mutations in the *ARPC1B* gene cause a syndromic combined immunodeficiency with congenital thrombocytopenia. In *ARPC1B* gene defect, micro-thrombocytopenia, decreased platelet dense granules, and platelet spreading defect with prominent filopodia but limited lamellipodia were characteristic features (PMID: 28368018) [4]. Platelets were small, similar to those with Wiskott–Aldrich syndrome. Several *ARPC1B* gene variants have been identified so far, and the clinical presentation varies, including elevated levels of immunoglobulin E (IgE) and immunoglobulin A (IgA), thrombocytopenia, and eosinophilia [4].

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Here, we describe a patient with persistent fever and recurrent marked peripheral blood eosinophilia. We identified a homozygous novel *ARPC1B* variant in this patient. Additionally, the patient has a concomitant compound heterozygous variant in the *CFTR* gene.

Presentation of case

A 2-month-old female patient was admitted to the hospital for recurrent fever, following a previous hospitalization at a local center for fever, bloody diarrhea, and vomiting, which were possibly due to sepsis. During the hospitalization, the patient received treatment with IV amikacin, vancomycin, and cefotaxime. Her diarrhea could be related to a food allergy, so we eliminated cow milk from the diet. Immunoglobulin levels were within the normal range, but immunodeficiency could still be present, and hypogammaglobulinemia may not have developed yet due to maternal antibodies. There was accompanying peripheral blood eosinophilia in the patient. Due to the possibility of multisystem inflammatory syndrome in children (MIS-C), intravenous immunoglobulin (IVIG) treatment was administered at a dose of 1 g/kg for two days. During the physical examination, Simian creases were present in both hands. The patient had blue sclerae, anteverted ears, a high palate, and a depressed nasal bridge.

The patient was admitted to the infectious disease department approximately two weeks later due to a high fever. She had eosinophilia in addition to increased liver function tests. Laboratory tests revealed a negative *Aspergillus* antigen test and CMV at 5149 copies/mL. The patient received approximately one month of ganciclovir treatment. An eye examination showed normal findings for retinitis. Abdominal ultrasound was not compatible with hepatitis. Although the fever subsided, CRP levels did not decrease, and leukocytosis was present. Fig. 1A shows the patient's thorax CT scan results. Upon observing a hemoglobin level of 6.4 g/dL, the patient received four times erythrocyte suspension. The patient's Direct Coombs test was negative. Also, the patient had bacteremia with *Enterococcus faecalis*, and we initiated sulbactam/ampicillin.

Subsequently, the patient experienced an eosinophilia episode. She had oral thrush, and the swallowing difficulty could be due to eosinophilic esophagitis due to candidiasis. Eosinophilia resolved with fluconazole, and endoscopy was not required. The patient had another eosinophilia episode, this time shortly after perioral herpetic lesions. Coin-sized rashes occasionally appeared on the patient's face, accompanied by a fever lasting about three days. The lesions on the cheeks were similar to herpetic lesions (Fig. 1B), and we started acyclovir. Eosinophil counts decreased with acyclovir treatment, and the skin lesions disappeared. The peripheral blood smear did not reveal any atypical cells, and the results were as follows: 4% eosinophils, 10% monocytes, 30% neutrophils, and 54% lymphocytes. Bone marrow aspiration and cytogenetic analysis were normal. We gave the laboratory parameters in Table 1. We observed a slight increase in effector memory T cells together with leukocytosis, eosinophilia, increased naïve, decreased switched memory B cells, decreased naïve, increased TEMRA, and effector memory CD8$^+$ T cells, and decreased central memory T helper cells.

The family has no known metabolic or immunodeficiency disease (Fig. 1C). The patient had compound heterozygous CFTR variants with sweat chloride test in normal limits. After identifying the *ARPC1B* gene variant, we planned hematopoietic stem cell transplantation. Donor screening revealed an HLA-matched donor. She is now 15-months-old, under IVIG therapy, and waiting for HSCT.

Genetic analysis

Given the phenotype and severity of the symptoms, we considered a primary immunodeficiency and performed whole-exome sequencing (WES). The analysis revealed a variant in the *ARPC1B* gene (c.1081-5T>G) (Fig. 2A) and compound heterozygous variants in the *CFTR* gene (c.3154T>G (p.Leu997Phe) and c.2991G>C (p.Phe1052Val)), both previously described [5–7]. Although there are some reported variants including homozygous c.783G>A (p.Ala261Ala), c.623_624delTC (p.V208fs), and c.622G>T (p.Val208Phe) [8,9] in the *ARPC1B* gene, homozygous c.1081-5T>G variant was novel and not previously reported in the literature. The variant was present in a region that is conserved among species (Fig. 2B).

Immunofluorescent staining

To test the possibility that the present novel *ARPC1B* gene variant found in the patient may affect protein function or not, fresh peripheral blood lymphocytes were stained with ARPC1B and DAPI and then analyzed using immunofluorescence microscopy (Axioplan, Zeiss). We used cytospins to have a monolayer of PBMC cells on glass slides. PBMCs were pipetted into each of the sample chambers of the cytospin and centrifuged at 300× *g* for 3 min (Thermo Shandon, USA). Cells were fixed for 10 min in 99% ethanol and stored at 4 °C before staining. The slides were washed with PBS and blocked with Fc receptor blocker (INNOVEX, NB309, USA) and 0.1% Tween-20 (Merck, Germany) in PBS and incubated for 1 h at room temperature. Antibody dilution for ARPC1B was 1:500, and incubated for 1 h at room temperature (Invitrogen, PA5-28103, USA) and for secondary antibody, 1:1000 (Molecular Probes, A11036,

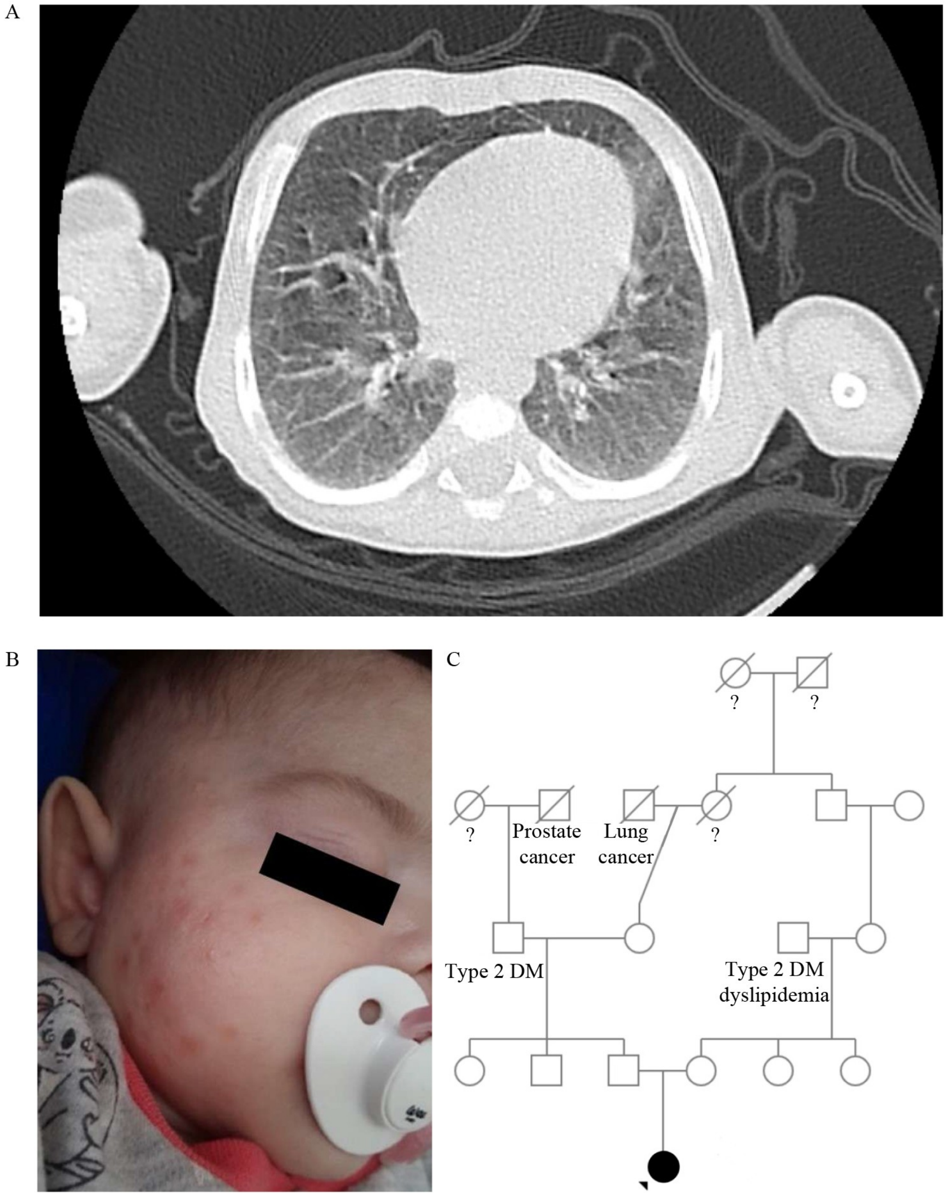

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Fig. 1 (A) Areas of focal low-density air trapping are observed in both lungs. A non-specific millimetric nodule is superimposed over the left major fissure. (B) The erythematous lesions appearing on the cheek. (C) Pedigree of the patient.

USA), and incubated for 40 min at room temperature. We added Prolong® Gold antifade with DAPI (Life Technologies, P36935, USA) coating solution to the slides and permanently closed them with a coverslip. We used a fluorescence microscope (Axioplan, Zeiss) to capture photographs. There was no ARPC1B expression in the patient cells (Fig. 3).

In silico analysis of variant

The *ARPC1B* gene variant was intronic (c.1081-5T>G), localized in intron 9 (Fig. 2B). *In silico* analyses reveal a combined annotation-dependent depletion score of 16.31 [10]. SpliceAI employs deep neural networks to forecast the likelihood of splicing events, assigning scores between 0 and 1 [11]. These scores indicate the probability of the variant causing alterations in splicing. The Δ score for acceptor loss of the identified variant was 0.42, suggesting a likelihood of acceptor loss occurring during mRNA splicing.

Discussion

Recent studies have uncovered a critical connection between cytoskeleton defects and immunodeficiency, highlighting the cytoskeleton's role in immune cell development, migration, and function. Disruptions in cytoskeletal elements have been linked to impaired

Table 1 Laboratory parameters of the patient

	Measured values	Normal values
Complete blood count		
RBC (×10^{6}/μL)	3.47	3.45–4.75
Hemoglobin (g/dL)	**9.4**	**9.9–12.4**
MCV (fL)	92.5	77–115
MPV (fL)	10.6	9–10.9
PLT (×10^{3}/μL)	237	150–450
WBC (×10^{3}/μL)	**25.8**	**6–17.5**
Eosinophils (×10^{3}/μL)	**0.94**	**0.02–0.58**
Lymphocytes (×10^{3}/μL)	**18.26**	**2.14–8.99**
Neutrophils (×10^{3}/μL)	5.44	1.04–7.2
Immunoglobulins		
IgG (mg/dL)	1030	294–1165
IgM (mg/dL)	74.3	33–154
IgA (mg/dL)	20.8	13.5–72
IgE (IU/mL)	3.5	1.5–144
Lymphocyte subsets		
CD3^{+} (%, ×10^{3}/μL)	75, 13.7	51–77, 2.5–5.6
CD4^{+} (%, ×10^{3}/μL)	39, 7.1	35–56, 1.8–4.0
CD8^{+} (%, ×10^{3}/μL)	**26, 4.7**	**12–23, 0.59–1.6**
CD16^{+} CD56^{+} (%, ×10^{3}/μL)	**18, 3.3**	**3–14, 0.17–1.1**
CD19^{+} (%, ×10^{3}/μL)	32, 5.9	11–41, 0.43–3.0
B cell subsets		
CD19^{+}CD27^{+} (%)	**3.8**	4.6–23.9
CD19^{+}CD27^{+} IgD^{+} (switched memory) (%)	**1.4**	**2.9–17.4**
CD19^{+}CD27^{+}IgD^{+} (marginal zone) (%)	2.4	1.7–6.5
CD19^{+}CD27^{-}IgD^{+} (naïve) (%)	**93.4**	**59.7–88.4**
CD19^{+} CD38^{+}CD21^{low} (active B) (%)	–	0.4–2.2
CD19^{+}CD38$^{+\ high}$IgM^{-} (plasmablasts) (%)	1.6	0.2–2.7
CD19^{+}CD38$^{+\ high}$IgM^{high} (transitional) (%)	6.8	4.1–43.9
T cell subsets		
CD4^{+}CCR7^{+}CD45RA (naïve T$_{H}$) (%)	72.4	57.1–84.9
CD4^{+}CCR7^{+}CD45RA^{-} (central memory T$_{H}$) (%)	**9**	**11.3–26.7**
CD4^{+}CCR7^{-}CD45RA^{-} (effector memory) (%)	13.2	3.3–15.2
CD4^{+}CCR7^{-}CD45RA^{+} (TEMRA) (%)	**5.1**	**0.4–2.6**
RTE (CD4^{+}CD45RA^{+}CD31^{+}) (%)	79	64–94
CD8^{+}CCR7^{+}CD45RA^{+} (Tc-naïve) (%)	**16.8**	**28.4–80.6**
CD8^{+}CCR7^{+}CD45RA^{-} (Tc central memory) (%)	2.7	1–4.5
CD8^{+} CCR7^{-}CD45RA^{-} (effector memory) (%)	**30.7**	**6.2–29.3**
CD8^{+}CCR7^{-}CD45RA^{+} (TEMRA) (%)	**49.6**	**9.1–49.1**

Values out of the reference range are indicated in bold font.

immune cell motility, adhesion, and phagocytosis, compromising the immune system's ability to respond against pathogens effectively. Actin remodeling defects can be elongation, transcription, branching, protrusion, and activation. Different gene defects affecting actin remodeling may present with diverse features. For example, patients with DOCK8 deficiency typically manifest symptoms early in their lives, including eczema, viral skin infections, persistent mucocutaneous candidiasis, bacterial pneumonia, and abscesses. Levels of antibodies in individuals with DOCK8 deficiency can vary, encompassing elevated/normal/reduced levels of IgG, IgA, and IgM. While IgE levels are typically high, there are cases with DOCK8 deficiency where IgE levels remain within the normal ranges [12]. The reduced quantity of T cell receptor excision circles (TRECs) observed in individuals with DOCK8 deficiency suggests that a diminished thymic output plays a role in patients' diminished numbers of naïve T cells [13]. Individuals with CARMIL2 deficiency exhibit stubborn warts, reduced counts of CD4^{+} and CD8^{+} memory T cells, and CD4^{+} regulatory T cells (Tregs) in their bloodstream [14].

Mutations in the gene responsible for encoding ARPC1B cause another immunodeficiency disease characterized by a combination of immunodeficiency, susceptibility to infections, allergic reactions, and inflammation. There are less than 50 cases in the medical literature, and the disease may present variously in affected individuals [4,8]. Among the reported cases, severe infections, eczema, recurrent otitis media, skin vasculitis, arthritis, food allergy, chronic CMV infection, asthma, hypothyroidism, and bleeding tendencies have been observed [4,15]. Thrombocytopenia and high IgE levels were present in a significant portion of patients [16]. However, thrombocytopenia and high IgE levels are absent in this case. Thrombocytopenia developed before age one in other cases reported in the literature. In contrast, it is not present in our patient, who is over one year old, attributed to the phenotype conferred by the variant in the *ARPC1B* gene.

Similar to other cases in the literature, our patient exhibited hypereosinophilia. Furthermore, we observed that the alterations in the eosinophil counts occurred during and after the infections (Fig. 4). Interestingly, when we initiated fluconazole treatment, suspecting that the patient's eosinophilia could be related to eosinophilic esophagitis, we observed an improvement in eosinophil counts. Therefore, we considered this supportive evidence for candida esophagitis. Also, the increased eosinophil levels associated with the herpes infection started to decrease upon initiating acyclovir treatment. When we examine the patient's T cell subsets, like DOCK8 deficiency, we observe a slight increase in memory T cells [13]. Hemoglobin levels decreased during the CMV infection due to bone marrow suppression, either infection- or drug-induced.

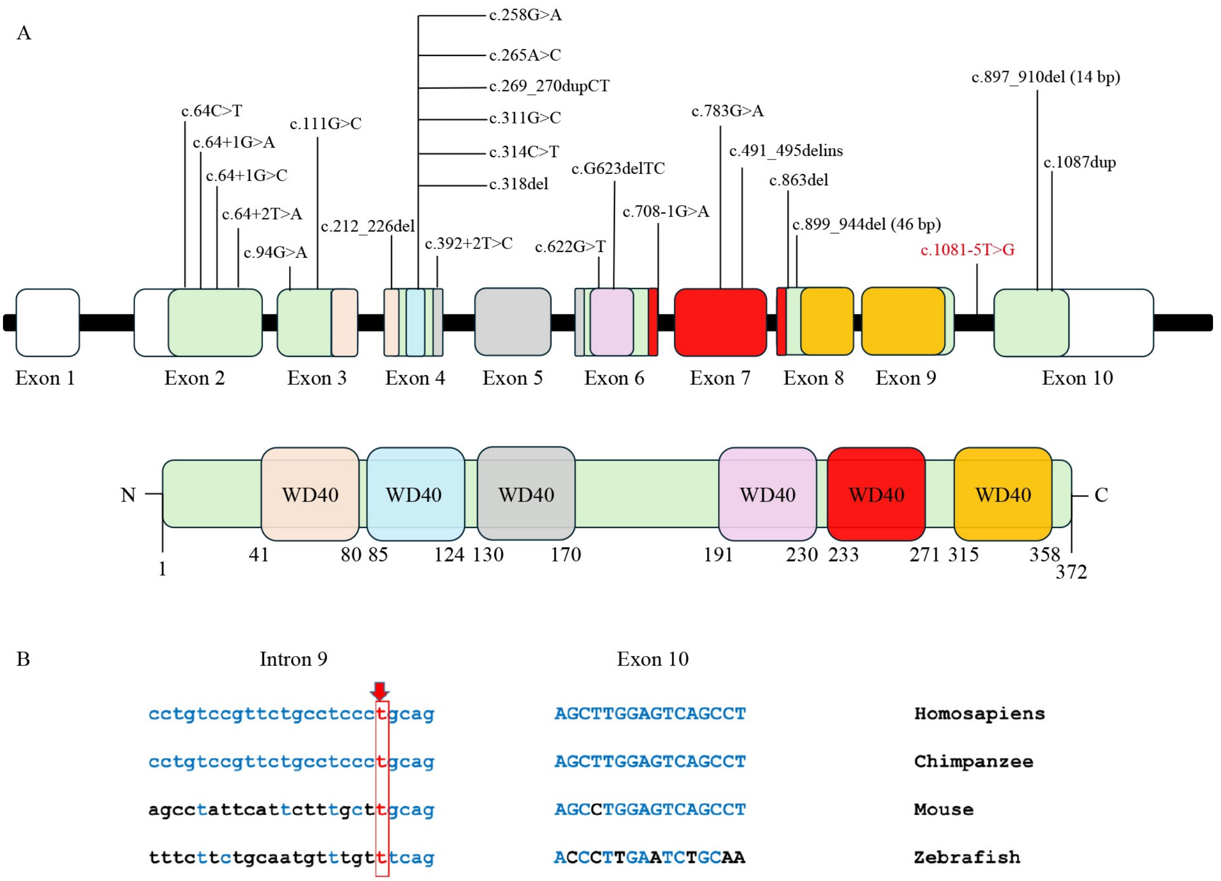

Fig. 2 (A) The variants of *ARPC1B* described in the literature are displayed, with the red-highlighted variant indicating the one identified in our patient. (B) The variant identified in our patient is located in a region that is highly conserved across species.

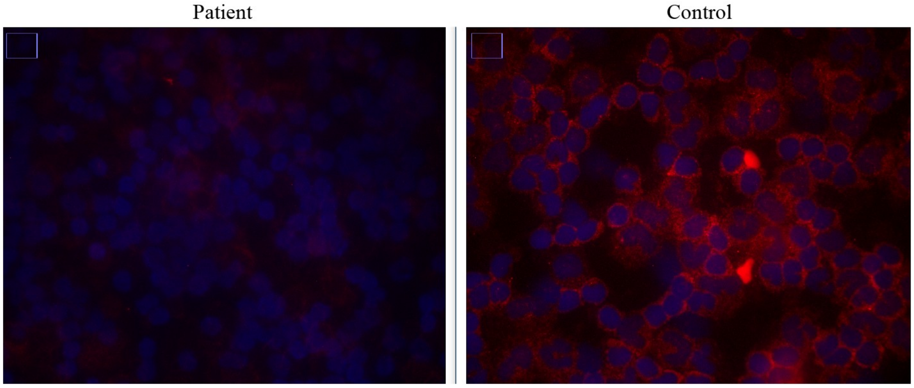

Fig. 3 Immunofluorescence microscopy of ARPC1B merged with nuclei (DAPI) in peripheral blood lymphocytes of our patient and control.

Mutations in the *CFTR* gene are widespread globally, and the patients may experience infections due to the formation of thick mucus in the lungs and intestines, leading to cystic fibrosis (CF). Cystic fibrosis was defined as leukocyte adhesion deficiency 4 (LAD-IV) since the disease affects neutrophil function [17]. In contrast to LAD-I, LAD-IV affects both β2 and α4β1 integrin proteins, leading to defects in monocyte adhesion and activation [4,18]. It leads to ongoing lung infections in individuals, gradually restricting their breathing ability. Patients also experience widespread bronchiectasis, bilateral congenital absence of the vas deferens, and chronic sinus inflammation [17]. In the present patient, we detected p.Leu997Phe and p.Phe1052Val variants of the *CFTR* gene. p.Leu997Phe substitution, in combination with other variations, was linked to recurrent pancreatitis, hypertrypsinemia in infants, and non-classical CF with recurrent pneumonia [5]. It is said to be challenging to

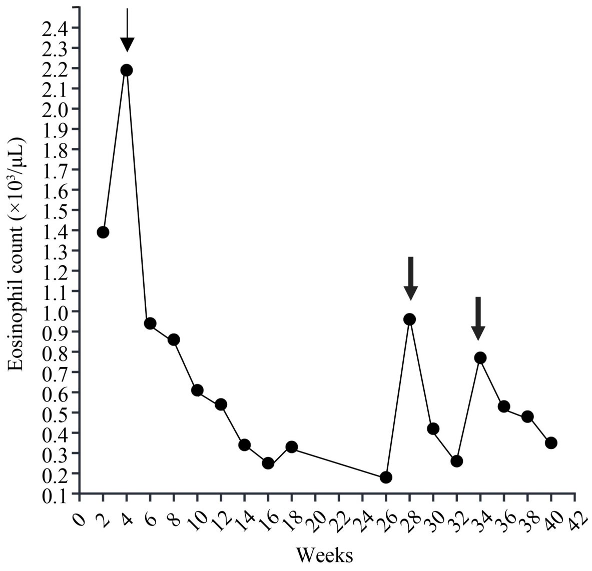

Fig. 4 The first arrow indicates a decrease in eosinophil counts following the initiation of ganciclovir treatment for CMV infection. The second arrow shows a decline in eosinophil counts after fluconazole therapy for *Candida albicans* infection. The third arrow reflects a subsequent reduction in eosinophil counts following the initiation of acyclovir treatment for herpes infection. (The reference range for eosinophil counts is 0.02×10^3–0.58×10^3/μL.)

consider it a causative mutation for CF [19]. p.Phe1052Val alteration was found in individuals with intermediate or normal sweat chloride levels, functioning pancreas, and rheumatoid arthritis-associated diffuse bronchiectasis [6,7,20]. It was also found in patients with CF, both in the homozygous state and in combination with another pathogenic mutation [21,22].

Patients with CF may experience eosinophilia in their disease course due to infections. The most common concomitant problem is allergic bronchopulmonary aspergillosis (ABPA) [23]. However, we did not detect *Aspergillus* antigen in the present patient. The sweat chloride test may be within normal limits in specific *CFTR* mutations in the medical literature, and technical issues, hypo-hydrotic ectodermal dysplasia, improper sweat collection, treatment with mineralocorticoids, infancy, swelling, low protein levels, and use of penicillin may cause a negative sweat test [24]. We thought that our patient's young age and the mutation type may be the cause of the sweat test result.

The immunofluorescent staining revealed an absence of ARPC1B expression in the patient, confirming the pathogenicity of the identified homozygous *ARPC1B* mutation. This finding is significant as it underscores the role of ARPC1B in immune cell function and its contribution to the patient's clinical phenotype, including recurrent eosinophilia and immunodeficiency. The absence of ARPC1B highlights its crucial role in actin polymerization and immune cell maintenance. The data suggest that ARPC1B deficiency disrupts normal cellular functions, leading to immune dysregulation and increased infection susceptibility.

In conclusion, this case report sheds light on the intricate genetic mechanisms influencing immune function and emphasizes the requirement of a collaborative approach in managing patients with rare and complex genetic disorders. While there is no specific treatment modality, hematopoietic stem cell transplantation appears as an option for treatment, and it was effective in improving symptoms in a documented case series with ARPC1B deficiency [15]. Results provide a clear link between genetic mutations and clinical manifestations, supporting the need for further research into targeted therapies that can mitigate these effects. Further research into the underlying pathophysiology and potential targeted therapies will improve the prognosis and quality of life for individuals with such conditions.

Compliance with ethics guidelines

Conflicts of interest Gamze Sonmez, Baris Ulum, Ates Kutay Tenekeci, Canan Caka, Ali Şahin, Alp Kazancıoğlu, Begum Ozbek, İsmail Yaz, Saliha Esenboğa, and Deniz Çağdaş declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Informed consent was obtained from the family for publication of this report. Other ethical board approval is not applicable in this case report.

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