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Review Article

Peripheral eosinophilia in primary immunodeficiencies of actin dysregulation: A case series of Wiskott-Aldrich syndrome, CARMIL2 and DOCK8 deficiency and review of the literature

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1. Introduction

Actin filaments are polymerized proteins of actin monomers that play a critical role in cellular interactions and structure. Such roles include cell motility, cell division, vesicle trafficking, and cell signaling [1,2,35–37]. While widespread defects in cytoskeletal regulation may be catastrophic and result in embryonic lethality, a subset of cytoskeletal regulatory elements show expression relatively limited to the hematopoietic compartment [2-4]. Mutation in genes that regulate and control actin formation, of which Wiskott-Aldrich syndrome (WAS) is the prototype, may result in primary immunodeficiencies (PID) [5,6]. Many of these PIDs due to actin dysregulation have peripheral eosinophilia as a common manifestation of the disease [2]. Due to the central role of actin filaments in cell interaction, immune synapse formation, and proliferation, a defect can affect many components of the immune system. Thus, actin dysregulation adversely affects immune response [2]. Affecting these aspects are a multitude of proteins that serve as regulators in actin formation.

In this paper, we highlight three disease entities by way of three different cases and clarify the connection between the causes of actin dysregulation leading to peripheral eosinophilia by synthesizing available literature in this area and relating it to the potential underlying mechanisms of immune dysfunction. Two of the cases involve the regulation of actin polymerization associated with T cell receptor (TCR) ligation. Wiskott-Aldrich syndrome protein (WASp) and dedicator of cytokinesis 8 (DOCK8) both serve as regulators actin polymerization by way of ARP2/3 with DOCK8 being critical for WASp activation (Fig. 1) [7–9,34]. The third case involves homozygous mutation of the Capping Protein Regulator and Myosin 1 Linker 2 (CARMIL2), which affects the capping of the actin filament and CD28 co-stimulation. All three entities lead to a defect in actin formation and are required for normal TCR signaling (Fig. 1). This then produces an abnormal T helper 2 (Th2) immune response while down regulating the Th1 response leading to peripheral eosinophilia [4].

While these entities share clinical features of immune deficiency, atopy, and eosinophilia, the disease manifestations of these patients also differ. Their severity differs based upon a variety of factors, including between patients within the same disease category. The specific underlying mutation, the range of cell types affected, the extent to which the encoded protein expression is decreased by the mutation, and the precise role of the protein in actin regulation all potentially produce varying manifestations of immune deficiency even though all three entities act on actin regulation.

This case series highlights the importance of not only actin filaments in the regulation of immune function but also the regulators in actin filament production. Actin filament production, maintenance, and breakdown is a highly dynamic and elaborate process with alteration of even a single protein having widespread effects. While three specific cases of actin filament dysregulation are highlighted, many more may exist in this complex system.

2. Materials and methods

Following institutional review board approval, the pathology archives at Weill Cornell Medical Center/New York Presbyterial Hospital, New York, USA were searched to identify patients with a primary immune deficiency disorder who had tissue sent for evaluation. In addition, one patient with DOCK8-deficiency syndrome was identified from the pathology archives at Hacettepe University, Ankara, Turkey. Relevant clinical and laboratory details for each patient were collected from available medical records.

3. Clinical history

3.1. Case 1

A male baby presented at birth with thrombocytopenia and a diffuse petechial rash throughout his body. In addition, he had a positive urine

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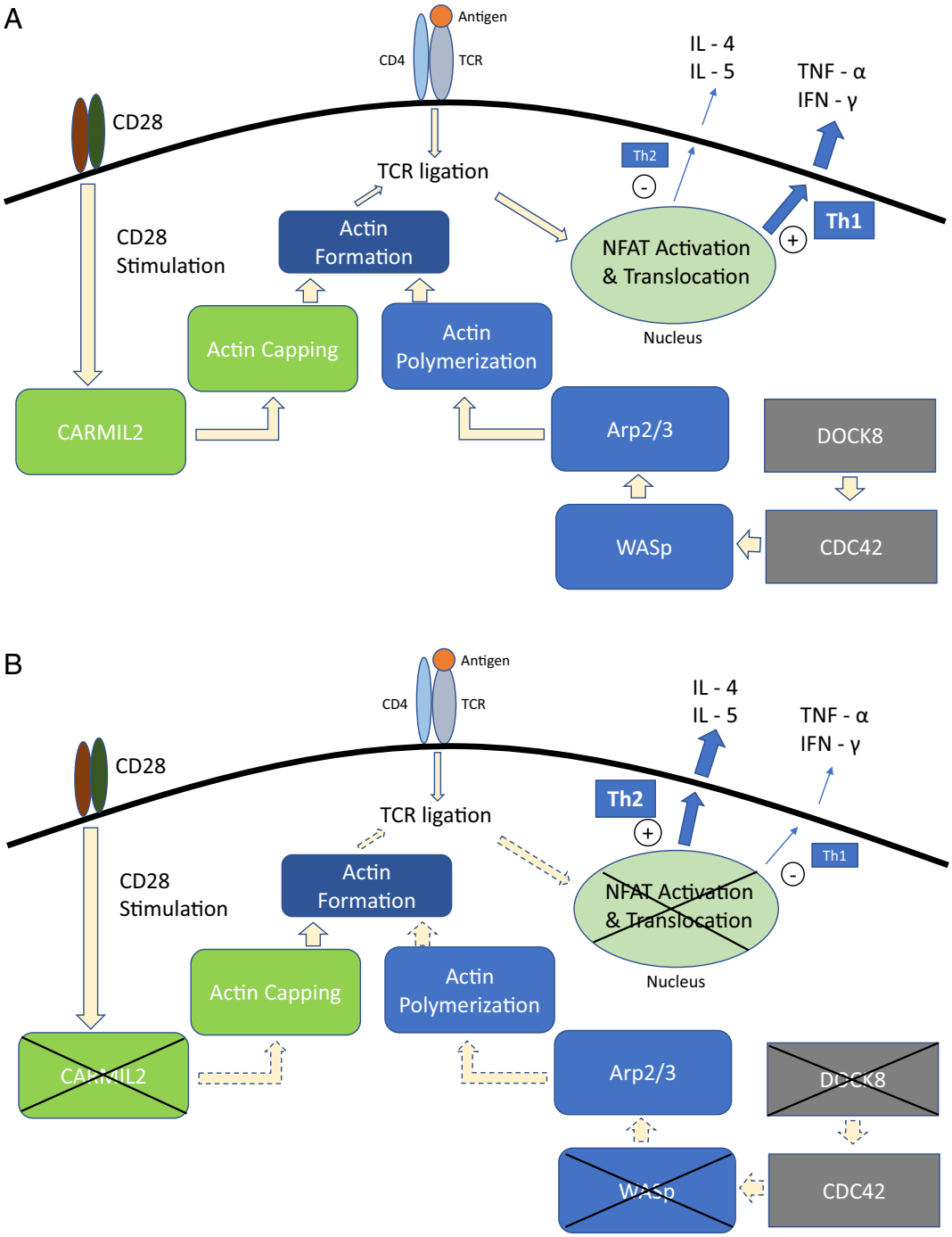

Fig. 1. Regulation of the cytoskeleton in immune synapse formation. The proteins CARMIL2, ARP2/3, and DOCK8 all contribute to actin formation as shown in this diagram. Actin formation is integral in T-cell receptor signaling that leads to NFAT activation in the nucleus. The activation of NFAT in non-mutated cells results in Th1 and Th2 regulation in uninvolved cells with a relative Th1 predominant cytokine response (A). When CARMIL2, WASp, and/or DOCK8 is mutated this signaling pathway is disrupted, which results in overexpression of the Th2 pathway and cytokines that upregulate eosinophil proliferation (B).

for cytomegalovirus (CMV) and high CMV IgM titers at birth. Platelet counts in his first year ranged from 10,000–25,000/uL even with intravenous immunoglobulin (IVIG) and steroids. The obstetrical history was unremarkable with an uncomplicated vaginal delivery. Family history was non-contributory. A bone marrow biopsy at the age of one year revealed adequate megakaryocytes with normal trilineage maturation (Fig. 2). A peripheral smear demonstrated microthrombocytopenia. A cytogenetic study showed a normal male karyotype. No anti-platelet antibodies were detected. Due to the development of eczema on his arms bilaterally with findings of microthrombocytopenia, DNA testing was sent with a suspicion for WAS. The testing revealed a mutation in the second exon hotspot commonly found in the X-linked thrombocytopenia (XLT) region associated with WAS. Due to continued bruising and an episode of a minor GI bleed, a splenectomy was performed in order to stabilize his platelet counts. Description of the spleen is as below. A complete blood count at the time of the splenectomy revealed a hemoglobin of 9.1 g/dL, hematocrit of 27%, red cell distribution width of 16.8%, and a platelet count of 78,000/uL. Absolute eosinophil count was 0.16 and 1.9%. The patient was subsequently followed and treated with monthly IVIG

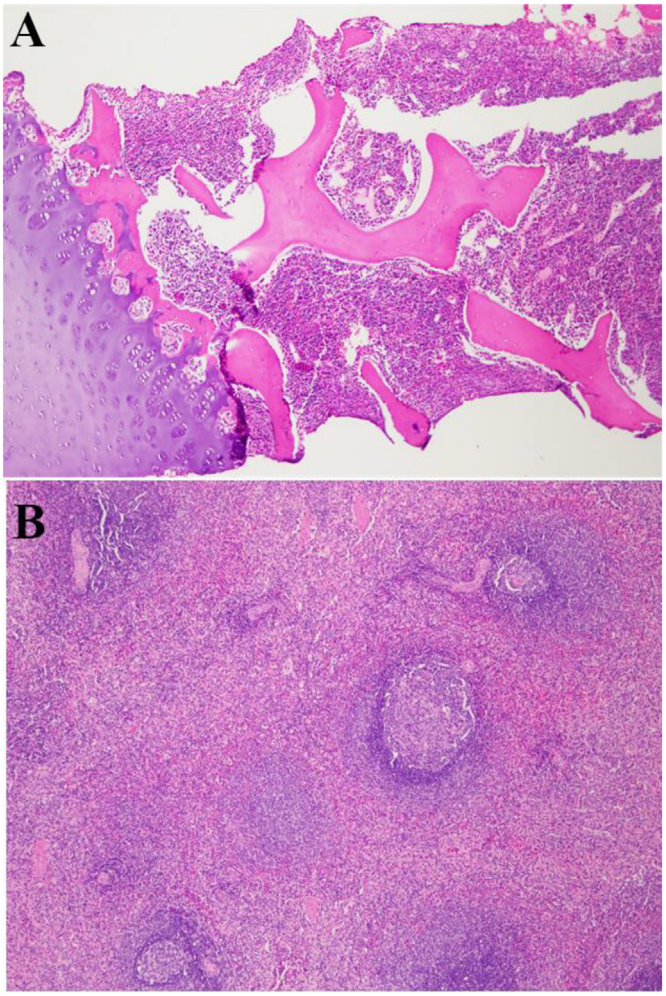

Fig. 2. Wiskott-Aldrich syndrome. Bone marrow trephine core biopsy specimen from a 1 year old boy with WAS demonstrated a normocellular bone marrow, typical of this entity despite the bone marrow homing defect of hematopoietic stem cells (A, 4× original magnification). A subsequent splenectomy specimen demonstrated variable lymphoid hyperplasia with focal attenuated marginal zones in the follicles (B, 10× original magnification).

Table 1
Laboratory values from the patient in case 1 (Wiskott-Aldrich syndrome) demonstrating the platelet response to splenectomy and subsequent development of eosinophilia over time.

Age (yrs)	WBC K/uL	Hb g/dL	Hct	Platelets K/uL	Eosinophils (%)
1	15.4	13	39%	11	3%
4	15.5	11	33%	21	1.3%
Splenectomy (age 4)					
9	10.5	12.9	39%	190	4.3%
19	10.6	16.3	47%	121	10.7%

infusions. No major events have occurred since the splenectomy except minor bleeds such as frequent nosebleed or gum bleeds. His platelet counts have also increased ranging from 150,000–175,000/uL. Elevations in his eosinophil count up to 2.10×10^3/uL also occurred (Table 1).

3.2. Case 2

The patient is a 4 year old female with an unremarkable birth history and uncomplicated vaginal delivery, who required multiple hospitalizations since birth for pneumonia, dysphagia, and anemia. She initially presented with multiple bouts of unexplained fevers and recurrent aspiration pneumonia. Additionally, after her routine childhood vaccinations there was an undetectable antibody response. Due to poor feeding with subsequent developmental delay, she required nasogastric tube feeds. Genetic testing was performed due to concerns for an immunodeficiency disorder or a glycogen storage disease. Testing revealed a homozygous pathogenic variant (c.1942delC) in the *CARMIL2* gene. Treatment included interval replacement of immunoglobulins. She underwent a gastrointestinal endoscopic series due to abdominal pain and bloody stools. Biopsy results revealed an ulcerated Epstein-Barr Virus (EBV)-associated smooth muscle neoplasm in the ascending colon (Fig. 3). In addition, the biopsies revealed pan colitis with diffuse eosinophilic infiltrates. Lab results were unremarkable with a WBC count of 14.4 × 10^3/uL, hemoglobin of 11 g/dL, and platelets of 329 k/uL. An auto-differential demonstrated a high eosinophil count of 2.5 × 10^3/uL with 17.6% eosinophils.

3.3. Case 3

The patient is a 12 year-old female (previously included as patient 2-1 in a series published by Sanal O. et al., which did not show detailed pathologic findings) [10]. She was born of a consanguineous family and presented initially at the age of 6 months with symptoms of atopic dermatitis. She developed skin lesions that were pink, hypopigmented and flat over the trunk and extremities resembling epidermodysplasia. In addition, she had recurrent herpes simplex virus infections as well as recurrent respiratory tract infections. At age 9, she developed a granulomatous lesion on her buccal mucosa. A biopsy revealed chronic granulomatous inflammation and ulceration. Treatment of the buccal lesion included debridement and corticosteroids. During a follow up of the buccal lesion, she developed dizziness and ataxia. On exam, she also had nystagmus, spasticity, increased deep tendon reflexes bilaterally, and developed a wide ataxic gait. A cranial MRI revealed bilateral T2 hyperintense lesions around the pulvinar as well as cerebellar and cerebral volume loss. BK and JC viral testing were negative. Subsequent cranial magnetic resonance imaging (MRI) studies revealed a rim enhancing restricted diffusion of the left temporo-occipital parenchyma. The lesion was initially thought to be an abscess and the patient was treated with wide-spectrum antibiotics and antifungals. However, the symptoms did not improve and an excisional biopsy revealed an EBV+ polymorphic lymphoproliferative process (Fig. 4). The patient's treatment course consisted of systemic chemotherapy, prednisolone, and cranial irradiation. Laboratory studies revealed low CD4 T cell levels with elevated CD8 T cell and NK cell levels. Additionally, the patient had elevated eosinophils, IgA, and IgE levels with low IgM levels. The patient's B cell levels were within reference range. The patient died four months after the diagnosis of the B cell lymphoma. Peripheral blood sequencing and array comparative genomic hybridization resulted in a *DOCK8* mutation. The patient's sibling also had a similar initial presentation with the same *DOCK8* mutation.

4. Gross and microscopic findings

4.1. Case 1

Peripheral smear demonstrated microthrombocytopenia. Bone marrow biopsy (age 1) demonstrated normocellular, trilineage hematopoiesis, mild lymphocytosis and adequate to mild megakaryocytic hyperplasia (Fig. 1). Eosinophils were relatively prominent. Cytogenetics demonstrated a normal male karyotype: 46, XY [20]. A splenectomy specimen (age 4) demonstrated lymphoid hyperplasia. Immunohistochemical stains of the spleen showed a mixture of B cell and T cells with relatively preserved white pulp. Focal B cell follicles with attenuated marginal zones (Fig. 1).

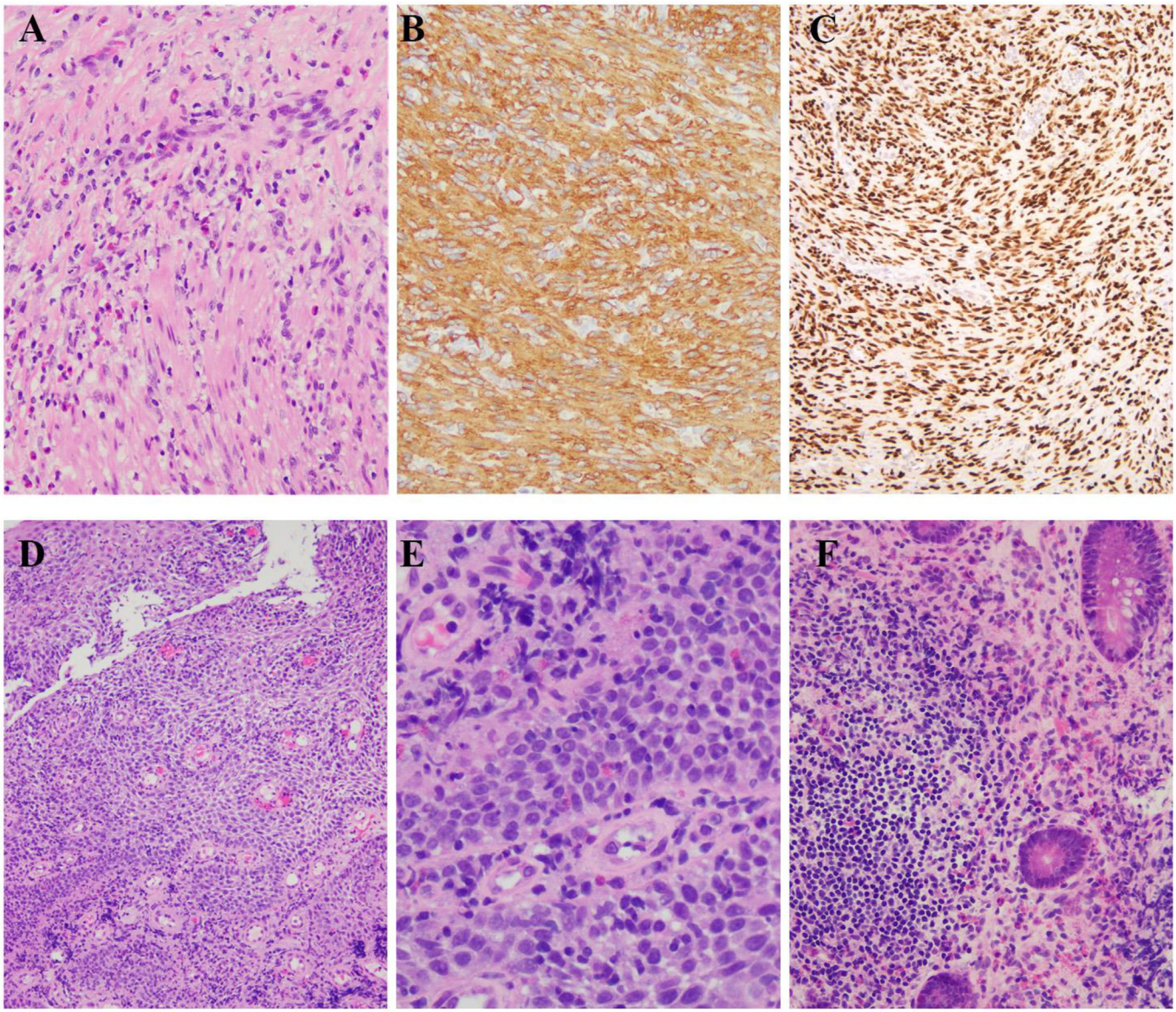

Fig. 3. CARMIL2 deficiency syndrome. EBV+ smooth muscle cell tumor in the colon of a 4 year old patient with CARMIL2 deficiency syndrome. Scattered eosinophils can be seen infiltrating the tumor (A), which is diffusely positive for smooth muscle actin (B) and EBER (C). The esophageal mucosa demonstrated a lymphocytic and eosinophilic infiltrate (D, E). Biopsies of the colon demonstrated pancolitis with eosinophilic and plasmacytic infiltrates (F). Photomicrographs for A, B, C and F at 20×, D at 10× and E at 40× original magnification.

4.2. Case 2

Endoscopic biopsy results revealed an ulcerated smooth muscle neoplasm in the ascending colon with numerous associated eosinophils (Fig. 2). The smooth muscle tumor was diffusely positive for EBER and smooth muscle actin. Scattered EBER+ cells were seen in the tonsils. In addition, the biopsies revealed pancolitis with eosinophilic and plasmacytic infiltrates. Esophageal biopsies demonstrated an increased lymphocytic infiltrate with scattered eosinophils. Rare *H. pylori* organisms identified in the stomach with a *H. pylori* stain confirming the presence of rare organisms.

Peripheral blood flow cytometry demonstrated: CD19, CD20+ polytypic B cells comprising 32% of lymphocytes. B cells showed partial dim expression of CD5 (42%) and CD10 (36%). CD3+ T cells comprise 46% of lymphocytes with a CD4:CD8 ratio of 1.4:1 and show no significant loss of pan T-cell antigens.

4.3. Case 3

A brain biopsy performed 1.8 years following onset of symptoms demonstrated an atypical lymphoid infiltrate with extensive necrosis. Perivascular cuffing was observed as well as more diffuse parenchymal invasion (Fig. 3). The infiltrate varied with some areas showing a more polymorphic appearance with scattered large atypical cells with background small to medium lymphoid cells. Focally increased plasma cells were also seen. The atypical cells were positive for CD20, CD30, MUM-1 and EBER without expression of CD10 or Bcl6. This case was reviewed as part of the 2015 Society of Hematopathology with a consensus diagnosis of polymorphic B-lymphoproliferative disorder, EBV+, DOCK8 deficiency, according to the proposed unifying nomenclature [11].

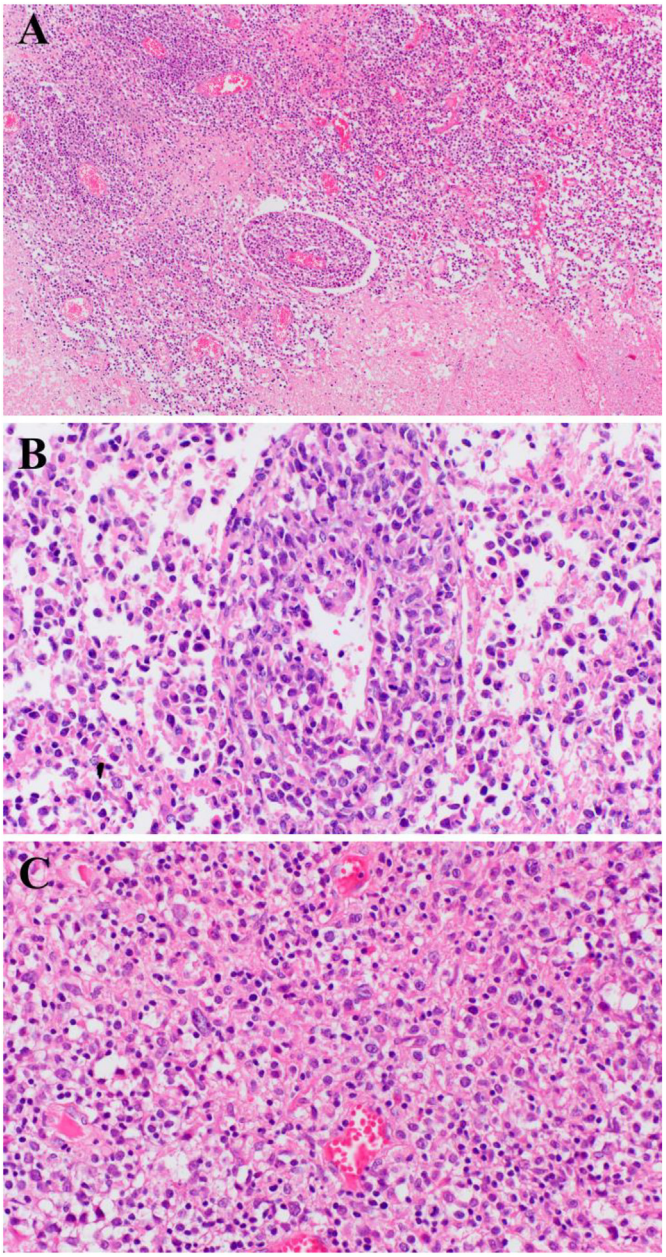

Fig. 4. DOCK8 deficiency syndrome. Sections of brain demonstrate an atypical lymphoid infiltrate most preserved around vascular structures with areas of necrosis (A, 10× original magnification). Perivascular cuffing is also highlighted in B, 40× original magnification. The infiltrate was relatively polymorphous (C, 40× original magnification). The atypical lymphoid cells were positive for EBV (not shown).

5. Molecular findings

5.1. Case 1

Hemizygous missense mutation (c.134C > T p.T45 M) of the *WAS* gene. This mutation is in the second exon hotspot and can be seen in WAS or, more commonly, in the less severe form of the disease, X-linked thrombocytopenia [12]. WAS is a multi-domain protein that directly aids in the polymerization of actin filaments with expression isolated to the hematopoietic system.

5.2. Case 2

Whole exome analysis demonstrated a homozygous frameshift mutation (c.1942delC) in *CARMIL2* (Capping Protein Regulator and Myosin 1 Linker 2). This creates a premature stop codon with loss of normal protein function. CARMIL2 protein is involved in cytoskeletal organization and cell migration.

5.3. Case 3

DOCK8 sequencing and array comparative genomic hybridization were performed on peripheral blood mononuclear cells to reveal a homozygous c. 4698C > G to p. Thr1566X as well as a c. 2389A > G to p. Val797Met. This mutation induces a premature termination with probable nonsense-mediated decay of the DOCK8 protein.

6. Discussion

Eosinophilia is a common finding in primary immunodeficiencies and such a diagnosis should be entertained when encountered in the appropriate clinical setting. However, there are a variety of different etiologies and pathways in which primary immunodeficiencies present with eosinophilia [2,4,13]. We present three cases in which the main cause of the primary immunodeficiency and eosinophilia is a defect in regulation of the actin cytoskeleton due to mutations in *WAS*, *CARMIL2* or *DOCK8*. Several investigations have been made into how deficiencies in these proteins may alter immune function, but the system is complex as the majority of immune cells are affected–ranging from hematopoietic stem cells to mature lymphocytes, antigen presenting cells and effector cells [14]. Depending on their normal pattern of gene expression and reliance on individual signaling pathways, hematolymphoid cells vary in the extent to which they show altered function such as abnormal cell signaling, migratory capacity, vesicle trafficking or phagocytosis of pathogens. We attempt to synthesize available literature to propose how the common pattern of eosinophilia and Th2-mediated atopy/allergic response emerges in the setting of acting cytoskeletal dysregulation.

Our first case is a patient with WAS, which is caused by a mutation in Wiskott-Aldrich Syndrome Protein (WASp), a multi-domain protein that directly aids in the polymerization of actin filaments with by regulating the actin nucleator Arp2/3 complex. WASp was the first of 8 members of this protein to be identified, and also is unique in its expression limited to the hematopoietic system. It is located on the X chromosome, and more than 300 mutations in this gene have been described. These mutations cause a range severity of presentations of this disorder generally related to extent of WASp deficiency, as well as a separate disorder, X-linked neutropenia, caused by distinct activating mutations [2,12,15].

WAS is well known to have associated peripheral eosinophilia as in our case [5,16]. One mechanism by which a mutation in the WAS protein can cause a downregulation of T-cell receptor signaling is through reduced stability of the immune synapse following its formation [17]. This may result in failure of immune activation. However, and importantly, strong affinity TCR peptide-MHC interactions produce a Th1 response while low-avidity promote Th2, creating a bias due to the weak interactions [18]. This may exacerbated by a failure to activate downstream TCR signaling. The translocation of the transcription factor of nuclear factor of activated T-cells (NFAT) to the nucleus requires the Ena-VASP homology domain (EVH1) of WASp, independently of the WASp regulation of the cytoskeleton [18]. This prevents the CD4+ cells in WAS to secrete normal amounts of Th1 cytokines which increases the relative amount of Th2 cytokines [2,6,19,37]. Thirdly, but also separate from the role in cytoskeletal regulation, WASp may localize to the *TBX21* gene, a master regulator of Th1 cytokine response, and be required for *TBX21* transcription [19].

Cytokines such as IL-4 and IL-5 from Th2 signaling induce an

increased eosinophil proliferation [20]. The eosinophils are early responders to this cytokine induction and appear to not only act as effectors of Th2 immunity but help create a self-perpetuating interplay with Th2 lymphocytes to aid in initiation and maintenance of the Th2 immune response [20]. They produce IL-4 and other Th2 cytokines and also inhibit Th1 lymphocytes by secreting indoleamine 2,3-dioxegnase.

Our second case is in a child with CARMIL2 deficiency due to homozygous mutation of the *CARMIL2* gene, which encodes a protein that is involved in cytoskeletal organization and cell migration. *CARMIL2* mutations and their sequelae have been cited in only a handful of case reports, but it results in a combined immunodeficiency that presents with dermatitis, esophagitis, recurrent skin and chest infections, as well as an increased risk for EBV-associated smooth muscle tumors [21]. In regards to immune function, CARMIL2 deficiency, like decreased WASp, dysregulates cell to cell signaling by actin dysregulation. CARMIL family proteins are large, multidomain proteins that directly bind capping protein (the 'C' in CARMIL), which regulates actin filament barbed ends. The Arp2/3 complex is unique for forming branched networks, and the capping protein contributes to and restricts the network architecture [22]. More specifically within this framework, CARMIL2 is required for CD28 co-signaling in T-cells for subsequent maturation and function and is a key component in T-cell cytoskeletal organization [23]. With a significant loss in CD28 co-signaling T regulatory (Treg) cells cannot develop as CD28 signaling is needed for Treg to mature from naïve $CD4^+$ T cells. As a result, with CARMIL-2 deficiency there is a deficiency with Th1 and Th17 cytokine production with a bias toward Th2 signaling [24]. This results in the associated eosinophilia.

Our third case demonstrated a patient with a homozygous missense mutation in the *DOCK8* gene that lead to a loss of function mutation in the DOCK8 protein. DOCK8 works closely with WASp in actin polymerization as a guanine nucleotide exchange factor for the Rho GTPase Cdc42 [8,25]. DOCK8 is linked to WASp through the WASp interacting protein (WIP), which also stabilizes WASp from degradation, and itself can result in a primary immune deficiency syndrome identical to WAS when deficient [2,26]. TCR ligation activates DOCK8 to promote its guanine nucleotide exchange factor activity for Cdc42 (GDP exchanged for GTP). The Cdc42-GTP activated form can then bind to WASp resulting in an open confirmation and ability of WASp to bind Arp2/3. The Arp2/3 complex then polymerizes new actin filaments on existing filaments [27,38,39]. Decreased DOCK8 function would decrease the activation of WASp and contribute similarly to actin dysregulation and increased Th2 cytokine production and eosinophilic response as with *WAS* mutation. [28]. This would also explain the decreased fraction of $CD4^+$ T-cells that was identified within the patient. However, the clinical manifestations and the Th2 response are more marked in this disorder, which was originally described as an autosomal recessive form of hyper IgE syndrome with severe combined immunodeficiency [29].

These three primary immune deficiency syndromes, DOCK8 deficiency, WAS, and CARMIL2 deficiency, all share clinical and pathologic features of peripheral eosinophilia, cutaneous manifestations such as eczema or atopic dermatitis, as well as increased levels of IgE with decreased levels of IgM. In addition, due to their susceptibility to viral infections these patients are at a greater risk for malignancies associated with viral infections such as EBV driven lymphomas or soft tissue tumors. These similarities would be expected in their shared responsibility in actin regulation.

However, the severity of the disease manifestations differs between these entities in terms of Th2 manifestations, immune dysfunction and susceptibility to viral infections. WAS patients typically have a milder immunodeficiency with a lesser degree of viral reactivation or viral-driven lymphoproliferative disease as compared to DOCK8 or the limited number of CARMIL2 patients who have been studied. The atopic responses in WAS patients are also attenuated compared to DOCK8-deficient patients, who more frequently show severe food allergy and anaphylaxis [29]. One contributing factor may be differing levels of redundancy for the role of these proteins in key allergy effector cells such as mast cells [18]. WASp is required for normal Kit signaling and Kit-mediated gene expression as well as for the cytoskeletal processes that enable IgE-mediated mast cell degranulation [30]. As such, the Th2 bias in these patients is not fully manifested due to the attenuated response of the mast cells to stimuli. Supporting this idea, conditional deletion of WAS from Tregs in a WAS mouse model resulted in a more severe Th2-type intestinal inflammatory response than global WASp deficiency [31]. By contrast, DOCK8 appears to be more dispensable for mast cell function with retained mast cell function in the setting of the Th2 bias and hyper-IgE resulting in more frequent anaphylaxis [18,32]. Nonetheless, WAS patients still develop exaggerated IgE-mediated reactions to common food allergens [31].

Other differences exist in their inheritance in that WAS is an X-linked recessive disease while *DOCK8* and *CARMIL2* mutations are autosomal recessive. Additionally, patients with WAS characteristically develop thrombocytopenia with small platelets. This leads to symptoms of bleeding, petechiae, and ecchymosis not often seen in DOCK8 and CARMIL2 deficiency syndromes. WAS and DOCK8-deficiency patients share symptoms of vasculitis and aortic aneurysms that are not seen in CARMIL2-deficiency. However, DOCK8 and CARMIL2 patients share symptoms of recurrent *Staphylococcus* skin infections and abscesses [33].

Actin filaments play an integral role in a multitude of pathways in normal cell function such as cell movement, division, and polarization. Regulation of actin polymerization is critical for cell signaling and immune cell differentiation and function. While a complex network of proteins are involved in this process, a subset show relatively specific expression within the immune system. Deficiencies in these proteins have been associated with primary immune deficiency syndromes. In this report, we highlight three such primary immune deficiencies associated with actin dysregulation and mutations in *WAS*, *DOCK8* and *CARMIL2*. All three patients had recurrent bouts of infections due to immune dysfunction starting from a young age, had symptoms of allergy and atopy and developed peripheral eosinophilia. The exact mechanism of hypereosinophilia in these entities are still being elucidated; however, abnormal immune synapse formation and disruption of downstream signaling required for normal T cell activation appears to be a key component of all three disorders. The subsequent bias toward Th2 cytokine production results in eosinophilia, which may function both as effector cells of the allergy and atopy in these patients as well as helping to perpetuate an abnormal Th2 bias in immune response.

While primary immune deficiency syndromes are rare, their evaluation yields insight into normal immune function, tolerance and surveillance of tumors and pathogens. Regulation of the actin cytoskeleton is a dynamic and critical component of these processes and with better understanding may be amenable to manipulation in disease states.

Authors' contributions

David Kim M.D.: Conceptualization, methodology, investigation, writing – original draft, writing – review & editing, and visualization.

Aysegul Uner, M.D.: Investigation.

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Genevieve M. Crane M.D., Ph.D: Conceptualization, methodology, investigation, writing – original draft, writing – review & editing, visualization, and supervision.

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Declaration of competing interest

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