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LETTER TO EDITOR

CADINS in an Adult with Chronic Sinusitis and Atopic Disease

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The CARD11/BCL10/MALT1 (CBM) complex is a critical signalosome in lymphocytes that facilitates several downstream immune responses, predominantly through activation of the transcription factor NF-κB. Although loss of function (LOF) CARD11 mutations cause profound combined immunodeficiency, heterozygous dominant-negative (DN) mutations may result in a clinical entity collectively referred to as CARD11-associated atopy with dominant interference of NF-κB signaling (CADINS) [1]. CADINS is associated with a range of clinical manifestations including allergic disease and frequent infections that may resemble other primary immunodeficiency disorders (PID). Atopy is the most common finding in CADINS, reported in close to 90% of cases, followed by cutaneous viral infections, respiratory infections, and autoimmunity [2].

A 31-year-old female presented with asthma, atopic dermatitis, allergic rhinitis, and a history of episodic fatigue and sinusitis for several years. Episodic fatigue occurred every 2–3 weeks and was described as not feeling rested even after 12 h of sleep. Chronic sinusitis was treated with 4–5 prolonged antibiotic courses per year. Nasal cultures grew methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* and *Haemophilus influenzae*. Three separate sinus surgeries over the prior few years moderately reduced her sinus symptoms. Other relevant history was significant for recurrent urinary tract infections with *E. coli* and Klebsiella, recurrent otitis media as a child, and a diagnosis of transient hypogammaglobulinemia of infancy that resolved at 4 years of age.

Review of systems revealed intermittent axillary lymphadenopathy, longstanding eczema that responded to topical tacrolimus, multiple environmental allergies, and recently diagnosed asthma that improved with inhaled budesonide/formoterol. As a teenager, she received allergen immunotherapy (AIT) for a few years but stopped due to frequent adverse reactions. Family history revealed that her mother received AIT for seasonal allergies, and her father died from infection associated with chemotherapy for non-Hodgkin's lymphoma. Physical exam at the initial evaluation was only remarkable for nasal turbinate hypertrophy.

Laboratory evaluation demonstrated normal IgG 886 mg/dL, IgM 139 mg/dL, IgA 156 mg/dL, elevated IgE 373 kU/L, normal T and NK cell enumeration, slightly decreased total B cells (180 cells/μL, 5.6% of lymphocytes), and normal B cell subsets ($CD19^+$ $CD27^-IgM^+$ 67%, $CD19^+$ $CD27^+IgM^+$ 17%, $CD19^+IgM^-CD27^+$ 13%). Tetanus antibody titer was protective (0.27 IU/mL), but Hib antibody titer was undetectable at < 0.15 IU/mL and not protective after vaccination (0.53 IU/mL). Pneumococcal serotype-specific IgG levels (Mayo Laboratories, Rochester, MN) were undetectable to 20 of 23 serotypes tested at baseline, and only 4 were considered protective post-vaccination with Pneumovax 23. QuantiFERON gold assays consistently showed IFN-γ release > 10.00 IU/mL in response to PHA (positive control), demonstrating T cell responsiveness to this mitogen. Due to poor antibody response and continued sinus infections, she was started on IgG replacement for the diagnosis of specific antibody deficiency. Her fatigue and sinus symptoms improved moderately, but she continued to require antibiotics. Sinus CT scans continued to demonstrate significant disease. An in-house focused exome panel showed only a novel heterozygous CARD11 variant (c.215G>T, p.R72L).

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Both the patient's variant (p.R72L) and a previously reported pathogenic variant in the same amino acid (p.R72G) involve a change from a charged arginine to a non-polar amino acid in the critical BCL10/CARD11 binding interface [3]. To test the potential impact of this variant on CBM-driven NF-κB activation, we examined the degradation of IκBα after stimulation with PMA. We saw no degradation in B cells from this patient as compared to a healthy unrelated control (Fig. 1), confirming a functional defect in NF-κB signaling. To further investigate whether R72L was a LOF/DN variant, we tested ectopic expression and its ability to transduce signals leading to NF-κB-mediated transcription in a cell line assay [2]. The R72L variant construct or wild-type (WT) CARD11 was transfected into CARD11-deficient Jurkat cells (JPM50.6) that carry a stable NF-κB GFP reporter [2]. The R72L variant demonstrated comparable protein expression but significantly decreased NF-κB-driven GFP expression with both anti-CD3/CD28 and PMA/ionomycin stimulation compared to WT or empty vector (EV) control (Supplementary Fig. 1). To test whether this variant acted in a DN fashion, we co-transfected the R72L construct in a 50:50 ratio with WT CARD11. NK-κB-dependent GFP expression (Supplementary Fig. 2) and IL-2 secretion (Supplementary Fig. 3) were not rescued. Taken together, these results definitively identify R72L as a LOF/DN variant.

Our patient presented with asthma, allergic rhinitis, atopic dermatitis, recurrent sinus infections, and elevated IgE. Initially these findings seemed consistent with typical severe adult atopic disease. However, selective antibody deficiency and persistent sinus disease justified a search for a genetic cause. Patients with CADINS may present with typical atopic findings including atopic dermatitis (73%), asthma (55%), food allergies (32%), and eosinophilic esophagitis (7%) [2]. Laboratory studies typically show normal T cell counts, fewer class-switched memory B cells despite normal total B cells, elevated eosinophils, elevated IgE, and variable T cell proliferation and antibody response to vaccination [1]. Specific antibody deficiency as observed in our patient is commonly seen in CADINS, including patients harboring the closely related R72G variant [2]. Recent data from new mouse models suggest that B cell defects associated with germline CARD11 mutations may be linked to a noncanonical regulatory function on the AKT-FOXO1 signaling axis [4]. This connection should be explored in human patients in future studies. Nevertheless, our patient's history and demonstration of a novel R72L variant that dominantly interferes with normal NF-κB activation produced a definitive diagnosis of CADINS.

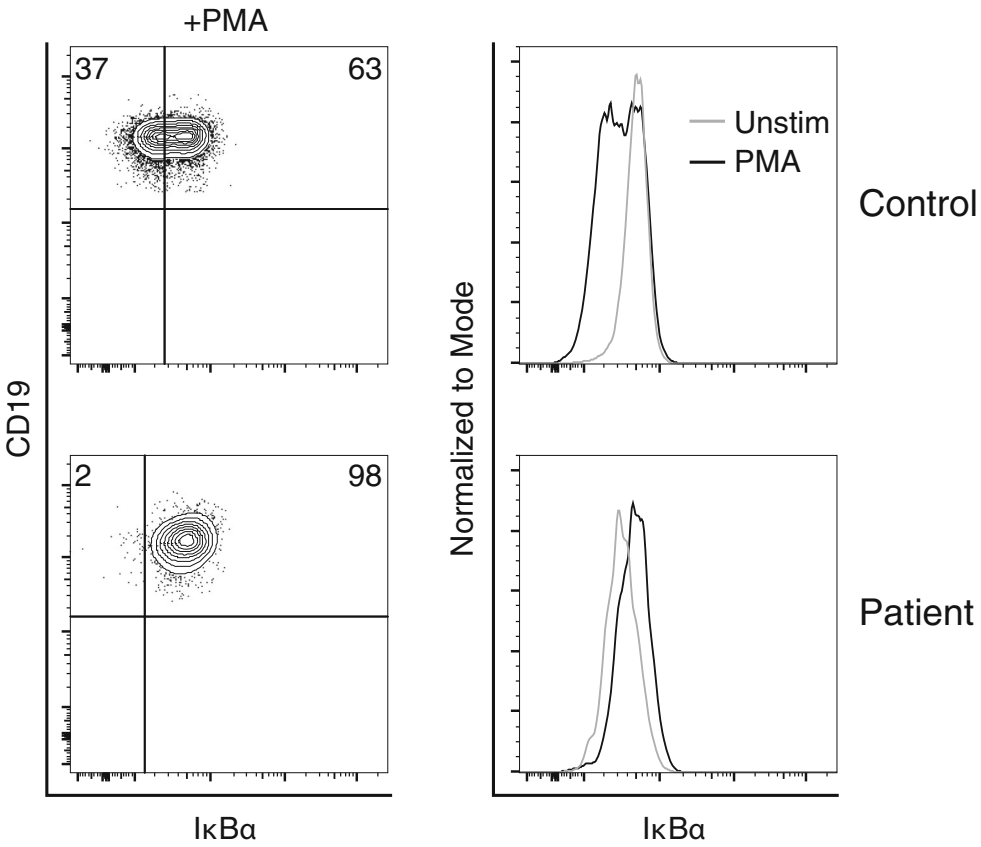

Fig. 1 Defective NF-kB activation in primary B cells from patient with CARD11 variant (p.R72L). We performed an IκBα degradation assay (fully described in the supplementary repository) for the patient compared to a control. Unstimulated B cell populations are depicted on the left. B cells were stimulated with phorbol 12-myristate 13-acetate (PMA) for 20 min. The patient demonstrates absent IκBα degradation compared to control (right column: light gray line, unstimulated; dark black line, PMA stimulated))

Increasingly, IgE-mediated allergic disease has been recognized as a feature of novel PIDs. Eczematous dermatitis is a common manifestation of several PIDs, including dedicator of cytokinesis 8 (DOCK8) deficiency, signal transducer and activator of transcription 3 (STAT3) deficiency, Wiskott-Aldrich syndrome, WIP deficiency, IL6ST deficiency, ZNF341 deficiency, ERBIN deficiency, APRC1B deficiency, PGM deficiency, Loeys-Dietz syndromes (TGFBR1 or TGFBR2 deficiency), and immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX). Of these disorders, DOCK8 deficiency (although more severe) may closely mimic CADINS, sharing atopic associations including food allergies and asthma and often presenting with cutaneous viral infections and recurrent respiratory infections [5]. Clinicians should be aware of CADINS when patients present with recurrent infections in the setting of significant allergic disease. Management of CADINS varies and may require a multi-pronged approach to address atopic, infectious, and autoimmune manifestations [5]. Antimicrobial prophylaxis and IVIG can be considered if infections are persistent or severe. Glutamine supplementation has shown some promise in vitro by restoring T cell proliferation and IFN-γ production in CARD11 DN cells [6]. Biologics targeting Th2 cytokine signaling, such as dupilumab or mepolizumab, might be useful in patients with severe refractory atopic disease, but further study is needed.

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Compliance with Ethical Standards

Conflict of Interest The authors declared that they have no conflict of interest.

References

1. Lu HY, Bauman BM, Arjunaraja S, Dorjbal B, Milner JD, Snow AL, et al. The CBM-opathies—a rapidly expanding spectrum of human inborn errors of immunity caused by mutations in the CARD11-BCL10-MALT1 complex. Front Immunol. 2018;9:2078.
2. Dorjbal B, Stinson JR, Ma CA, Weinreich MA, Miraghazadeh B, Hartberger JM, et al. Hypomorphic caspase activation and recruitment domain 11 (CARD11) mutations associated with diverse immunologic phenotypes with or without atopic disease. J Allergy Clin Immunol. 2019;143(4):1482–95.
3. Qiao Q, Yang C, Zheng C, Fontán L, David L, Yu X, et al. Structural architecture of the CARMA1/Bcl10/MALT1 signalosome: nucleation-induced filamentous assembly. Mol Cell. 2013;51(6):766–79.
4. Wei Z, Zhang Y, Chen J, et al. Pathogenic CARD11 mutations affect B cell development and differentiation through a noncanonical pathway. Sci Immunol. 2019;4(41). https://doi.org/10.1126/sciimmunol.aaw5618.
5. Lu HY, Biggs CM, Blanchard-Rohner G, Fung SY, Sharma M, Turvey SE. Germline CBM-opathies: from immunodeficiency to atopy. J Allergy Clin Immunol. 2019;143(5):1661–73.
6. Ma CA, Stinson JR, Zhang Y, Abbott JK, Weinreich MA, Hauk PJ, et al. Germline hypomorphic CARD11 mutations in severe atopic disease. Nat Genet. 2017;49(8):1192–201.