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Association of B-cell activating factor receptor deficiency with the P21R polymorphism and common variable immunodeficiency

Matthew Germinaro, MD*, Paul Reynolds, PhD[†], Vijaya Knight, PhD[†], and Rafeul Alam, MD, PhD^{*,‡}

Rafeul Alam: alamr@njhealth.org

*Division of Allergy & Immunology, National Jewish Health, Department of Medicine, Denver, Colorado

[†]Advanced Diagnostic Laboratories, National Jewish Health, Department of Medicine, Denver, Colorado

[‡]University of Colorado Denver, School of Medicine, Denver, Colorado

We present a case a P21R polymorphism of the B-cell activating factor (BAFF) receptor (BAFF-R) leading to BAFF-R deficiency and immunodeficiency, which was associated with immunodeficiency and a thymic mass, thus partially mimicking Good syndrome in its initial presentation. The patient developed recurrent sinopulmonary infections at the age of 23 years. The patient had 20 episodes of radiographically confirmed pneumonia and more than 10 episodes of acute sinusitis. He had multiple episodes of cholangitis that required endoscopic retrograde cholangiopancreatography. At 32 years of age, he was found to have severe hypogammaglobulinemia (IgG, 122 mg/dL; IgA and IgM, undetectable), diagnosed as having common variable immunodeficiency (CVID), and prescribed replacement intravenous immunoglobulin. Later intravenous immunoglobulin was transitioned to subcutaneous immunoglobulin. Consequently, he experienced a marked reduction in the frequency of infections. In the preceding year, he only received antibiotics on a single occasion for infectious diarrhea. His medical history was complicated by the following problems: granulomatous hepatitis, congenital aplastic right kidney, mild splenomegaly, recurrent iritis, hypertension, vitiligo, eczema, and asthma. There is no family history of immunodeficiency or consanguinity.

The patient was incidentally found to have an anterior mediastinal mass that measured 1.5 cm on chest computed tomography (Fig 1A). Positron emission tomography computed tomography results were negative. His pulmonologist followed the mass using serial imaging without overt change in size or appearance. Good and Varco¹ first described the association between thymoma and hypogammaglobulinemia in 1955. Although there are no consensus diagnostic criteria, a systematic review analyzing 152 patients with Good syndrome described it as a constellation of thymoma and hypogammaglobulinemia, low or absent B cells, variable defects in cell-mediated immunity with CD4 lymphopenia, and

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reduced T-cell proliferative responses.² The immunologic profile of our patient did not fit this characterization completely. He had normal CD19⁺ (192/ mL) and CD20⁺ (146/mL) B-cell counts, but low switched memory B cells (3.2%) and increased natural killer cell numbers (710/mL). The absolute number of CD3⁺, CD4⁺, and CD8⁺ T cells and T-cell proliferative responses to phytohemagglutinin, concanavalin A, pokeweed mitogen, tetanus, and *Candida* were normal.

Anterior mediastinal masses are more likely to be malignant compared with middle and posterior mediastinal masses.^{3,4} Complete thymectomy has a favorable effect on associated conditions, such as myasthenia gravis and pure red cell aplasia.² Unfortunately, thymectomy does not usually reverse the immunologic abnormalities. Our patient was referred to a surgical oncologist, who performed robotic assisted biopsy of the left thymic lesion. Biopsy revealed benign thymic tissue. Flow cytometric analysis of fresh tissue was consistent with normal thymic tissue without evidence of a hematopoietic neoplasm. The absence of thymoma excluded the diagnosis of Good syndrome.

To determine the molecular mechanism of his immunodeficiency, we sequenced all 3 exons of the BAFF-R (*TNFRSF13C*) gene, which revealed a previously identified P21R polymorphism (rs77874543 in the Single Nucleotide Polymorphism database) in exon 1 (Fig 1B). Flow cytometric analysis revealed a 76% reduction in the expression of BAFF-R (Fig 1C). B-cell survival depends on BAFF-R signaling, which activates nuclear factor- κ B2.⁵ Previously, a homozygous 24-bp in-frame deletion (del89–96) in the BAFF-R gene was reported in 2 siblings.⁶ Only one of those siblings had profoundly low IgG and IgM levels and antibody deficiency and had recurrent infections, including pneumonia. The other sibling had modestly reduced IgG and IgM levels but no recurrent infections, suggesting a variable penetrance. Mutational analysis of BAFF-R in 48 patients with CVID in another study identified 3 novel heterozygous variants leading to amino acid substitutions and 1 previously reported intronic variant.⁷ Interestingly, these variants, including the P21R variant, did not affect the expression of BAFF-R at the messenger RNA or protein level. In contrast, the P21R variant was associated with reduced BAFF-R expression in our patient. A more recent study found that homo- and heterozygous P21R mutation actually impaired assembly of BAFF-R into multimeric complexes, decreased binding to BAFF, and reduced nuclear factor- κ B2 activation.⁸ The P21R patients also had reduced B-cell proliferation in response to BAFF. Thus, these abnormalities could explain reduced BAFF-R expression and clinical immunodeficiency in our patient. Our patient also manifested certain features (eg, undetectable IgA and granulomatous hepatitis) that are not known to be associated with BAFF-R deficiency. The P21R polymorphism can be present in healthy individuals, albeit at a lower frequency.⁷ Thus, the P21R polymorphism alone cannot explain the clinical phenotype. CVID can be associated with mutations of *TACI*, *ICOS*, *TAPAI*, and *CD21*, which were not studied in our patient. We hypothesize that one of these gene defects and/or additional yet-to-be defined gene polymorphisms, working in concert, contribute to reduced BAFF-R expression, impaired immunoglobulin production, and immunodeficiency in CVID patients with the P21R polymorphism.

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Figure 1.

A, A sagittal view of a chest computed tomograph showing a small, well-circumscribed anterior mediastinal mass. B, Flow cytometric analysis of B-cell activating factor receptor (BAFF-R) expression on CD19⁺ blood B cells from the patient (green) and a healthy control (dark purple). Mean fluorescence intensity (MFI) of BAFF-R staining is shown in the parentheses. This test was repeated twice with similar results. C, Sequence trace showing heterozygosity of a C>G mutation, leading to the missense mutation P21R. Trace is 1 of 2 that supported the mutation; alignments of both traces and the consensus is above the trace. Sequence alignment and the display was generated by Bionumerics software (www.applied-maths.com).