Aplastic anemia in a patient with CVID due to NFKB1 haploinsufficiency

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Abstract Acquired aplastic anemia (AA) is a life-threatening bone marrow failure caused by an autoimmune cytotoxic T lymphocyte attack on hematopoietic stem and progenitor cells. Factors contributing to aberrant autoimmune activation in AA include a deficit of T regulatory cells and high levels of inflammatory cytokines. Several acquired conditions of immune dysregulation and genetic polymorphisms in inflammatory cytokines and human leukocyte antigen genes have been linked to an increased risk of AA. However, AA has not been reported in patients with Mendelian disorders of immune regulation. Here we report a patient with familial common variable immunodeficiency (CVID) caused by a pathogenic variant in NFKB1, who developed AA as an adult. The patient had a difficult clinical course and was unable to tolerate standard AA therapy with cyclosporine A and eltrombopag, with complications attributed in part to the effect of cyclosporine A on NF-κB signaling. Our case suggests a novel link between genetic disorders of immune regulation and AA and highlights the importance of recognizing inherited autoimmunity syndromes in AA patients for the selection of optimal therapy and prognostic counseling.

[Supplemental material is available for this article.]

INTRODUCTION

Acquired aplastic anemia (AA) is a rare life-threatening blood disease characterized pathologically by pancytopenia and a hypocellular bone marrow due to the immune-mediated destruction of early hematopoietic cells by cytotoxic T lymphocytes (Young 2018). Specific triggers of autoimmunity or the identities of autoantigens immunologically targeted in AA remain unknown. Several acquired conditions involving immune dysregulation have been linked to AA, such as Hodgkin lymphoma (Linaburg et al. 2019), immune checkpoint inhibitor therapy (Davis et al. 2019), thymoma (Gendron et al. 2020), autoimmune hepatitis (Brown et al. 1997), and eosinophilic fasciitis (de Masson et al. 2013). Additionally, a number of polymorphisms associated with overproduction of inflammatory cytokines (e.g., interferon-γ [Dufour et al. 2004]) and certain human leukocyte antigen genes (Nakao et al. 1994; Babushok et al. 2017; Zaimoku et al. 2017) have been linked to an increased risk of AA. However, AA has not been previously reported in patients with inherited diseases of immune dysregulation. Here, we report a patient with common variable immune deficiency (CVID) caused by a pathogenic variant in the NF-κB1 gene (NFKB1), who developed AA during
her adult life and clinically rapidly declined despite attempts at standard AA therapy. Our patient’s case suggests a new connection between the immune dysregulation seen in primary immunodeficiencies and AA. Furthermore, we propose that alterations in NF-κB signaling as well as the more general complications associated with CVID, including liver dysfunction and enteropathy, may present unique challenges in the management of AA with currently available therapeutics.

RESULTS

Clinical Presentation and Family History
A 50-yr-old female was referred for an evaluation of suspected AA. Her past medical history was notable for CVID, which was diagnosed at the age of 12 yr, after having frequent upper respiratory infections as a child, and was managed with monthly intravenous immunoglobulin (IVIG). The patient’s CVID-associated complications included a remote history of autoimmune hemolytic anemia, currently in remission, which was diagnosed in the patient’s 20s and was managed with a variety of immunosuppressants and splenectomy. In her 30s, the patient was diagnosed with Plummer–Vinson syndrome, a classical triad of iron deficiency, esophageal webs, and dysphagia, which has been associated with autoimmune disorders and carries an increased risk of squamous cell carcinoma of the oropharynx (Chisholm 1974; Messmann 2001). At the age of 38 yr, the patient developed a squamous cell carcinoma of the tongue, which was cured with surgical resection. She was subsequently well over the following 10 years, until 2 years prior to her current presentation when she developed anemia. Her initial evaluation was notable for a low reticulocyte count and a hypocellular marrow with an absence of erythroid precursors, consistent with acquired red cell aplasia. She was treated with corticosteroids and low-dose cyclosporine without response and eventually progressed to aplastic anemia.

The patient’s family history was notable for Northern European and English ancestry, two healthy sisters who were monozygotic twins, a mother who died from glioblastoma at the age of 68 yr, and a maternal aunt with multiple sclerosis.

On physical exam, the patient was a thin middle-aged woman, weighing 106 lbs at a height of 5’7”. Physical exam was notable for a well-healed partial glossectomy without evidence of tongue carcinoma recurrence and no oral lesions or leukoplakia. Sclera were icteric. Cardiopulmonary exam was normal. There was no lymphadenopathy or hepatosplenomegaly. Skin exam showed no rashes, café-au-lait spots, or hypo- or hyperpigmented lesions. There was no nail dystrophy. Musculoskeletal exam was normal, with no thumb or radial anomalies.

Laboratory studies revealed a white blood cell count of 4 × 10^9 cells/L with a normal leukocyte differential, normocytic anemia (hemoglobin of 7 g/dL; mean corpuscular volume of 88 fl), a low reticulocyte count of 22 × 10^9 cells/L, and severe thrombocytopenia (19 × 10^9 platelets/L). A bone marrow biopsy revealed a severely hypocellular bone marrow with marked trilineage hypoplasia and scattered lymphohistiocytic aggregates, consistent with AA (Fig. 1). Cytogenetic examination of the bone marrow demonstrated a normal karyotype and targeted massively parallel sequencing of genes commonly mutated in hematologic malignancies showed no clinically significant variants. Consistent with an immunodominant antigen-driven autoimmune process in AA, polymerase chain reaction (PCR) analysis of the T-cell receptor gamma chain gene revealed a monoclonal rearrangement within a much more prominent polyclonal background (Risitano et al. 2004). There was no immunophenotypic evidence of clonal lymphoproliferative disorder or pan-T-cell antigen loss. Flow cytometry for paroxysmal nocturnal hemoglobinuria (PNH) revealed a subclinical (0.39%) PNH clone in granulocytes. Extensive evaluation for alternative etiologies of the patient’s bone
marrow failure, including underlying viral infection or nutritional deficiency was unrevealing (Supplemental Table S1). Chromosome breakage of the patient’s peripheral blood lymphocytes in the presence of mitomycin C and diepoxybutane was normal. Telomere testing showed low median lymphocyte telomere lengths between the first and fifth percentile for age in total lymphocytes as well as in the naive and memory T-cell and natural killer (NK)-cell subsets. The low telomere length was interpreted to likely reflect telomere attrition because of the underlying autoimmunity; however, to exclude an atypical telomeropathy or another occult inherited marrow failure syndrome, whole-exome sequencing was requested. Given the clinical urgency, the patient was started on treatment with cyclosporine and eltrombopag for a presumed diagnosis of AA, while awaiting genetic testing results to determine more definitive therapy. An evaluation for allogeneic hematopoietic stem cell transplant was initiated. Unexpectedly, the patient was not able to tolerate cyclosporine at therapeutic doses, with an unusual degree of complications including progressive failure to thrive, >10 lb weight loss (~10% body weight), fatigue, generalized pain and weakness, and septicemia within 2–3 wk of therapeutic cyclosporine dosing, requiring hospitalization. Cyclosporine was discontinued. Progressive liver dysfunction with rising hyperbilirubinemia and ascites precluded therapy with eltrombopag. Whole-exome sequencing revealed no disease-associated variants in genes associated with inherited bone marrow failure syndrome, but identified a heterozygous variant in NFKB1 (Fig. 2; Table 1). Unfortunately, the patient continued to have a progressively deteriorating course and died within 4 mo of AA diagnosis from multiple complications, including recurrent neutropenic sepsis, severe malnutrition due to CVID-related enteropathy, and hepatic dysfunction.

**Variant Interpretation**

A constellation of a congenital immune deficiency, short lymphocyte telomere lengths, malnutrition, and progressive bone marrow failure was suspicious for an underlying inherited
bone marrow failure syndrome. To screen the patient for an inherited etiology of her bone marrow failure, we performed whole-exome sequencing including sequencing of mitochondrial DNA. One heterozygous pathogenic variant in exon 8 of the \textit{NFKB1} gene (p.V235Wfs\^\textasteriskcentered17, c.702delC) was identified (Fig. 2). There were two additional variants in a gene associated with bone marrow failure and immunologic disorders (Supplemental Table S2); however, these were determined not to contribute to the patient’s phenotype.

Two variants in the \textit{DOCK8} gene, linked to autosomal recessive hyper IgE syndrome, were located in \textit{cis} in the same allele and the patient lacked clinical features of hyper IgE syndrome with no eosinophilia, eczema, or recurrent viral infections. The identified pathogenic variant in \textit{NFKB1} is predicted to lead to \textit{NFKB1} haploinsufficiency because of protein truncation or nonsense-mediated mRNA decay. It has not been previously reported in association with CVID and has not been previously identified in population databases (Genomes

| Table 1. Genomic findings |
|--------------------------|
| **Gene** | **Disease** | **Mode of inheritance** | **Variant** | **Coding DNA** | **Zygosity** | **Inherited from** | **Variant classification** |
|----------|-------------|------------------------|-------------|----------------|-------------|-------------------|--------------------------|
| \textit{NFKB1} | Common variable immunodeficiency | Autosomal dominant | p.V235Wfs\^\textasteriskcentered17 | c.702delC | Heterozygous | Unknown | Pathogenic |

Figure 2. The pathogenic variant in the \textit{NFKB1} gene (c.702delC; p.V235Wfs\^\textasteriskcentered17) identified in a patient with CVID who developed AA as an adult. (A) Screenshot from Integrative Genome Viewer (IGV) showing a single-nucleotide deletion in the \textit{NFKB1} gene (c.702delC; black arrow). (B) Confirmatory Sanger sequencing demonstrating the region containing the frameshift mutation (black arrow; region is shown in reverse complement).
Project Consortium et al. 2015; Lek et al. 2016; Exome Variant Server, Genome aggregation database [gnomAD]). Although germline status of the \textit{NFKB1} variant in our patient was not formally verified in paired nonhematopoietic tissue, \textit{NFKB1} is not a known cancer gene (Sondka et al. 2018), and \textit{NFKB1} mutations have not been described in age-related clonal hematopoiesis (Genovese et al. 2014; Jaiswal et al. 2014). The patient’s clinical presentation (Table 2), together with a pathogenic heterozygous variant in \textit{NFKB1} detected in the patient’s peripheral blood, is most consistent with autosomal dominant CVID caused by a germline \textit{NFKB1} variant. The patient’s sisters (monozygotic twins) were negative for the variant, and the other family members were not tested. Given the family history of glioblastoma in the patient’s mother and multiple sclerosis in the maternal aunt, two conditions linked to NF-\kappa B dysregulation (Rajaraman et al. 2009; Mieczkowski et al. 2015; Cartwright et al. 2016; Kina et al. 2019; Zhou et al. 2020), the patient’s \textit{NFKB1} variant could have been inherited from the maternal side of her family; alternatively, the variant may have emerged de novo.

**DISCUSSION**

In this report, we present a patient with familial \textit{NFKB1}-associated CVID syndrome who developed AA in adulthood. Although CVID can be associated with a variety of autoimmune complications, including autoimmune cytopenias such as immune thrombocytopenia (ITP), hemolytic anemia, Evans syndrome, and autoimmune neutropenia (Podjasek and Abraham 2012), neither immune-mediated bone marrow failure nor AA have been previously reported. The patient was unable to tolerate standard AA therapies and rapidly declined. Our case highlights the importance of recognizing inherited syndromes of immune dysregulation such as CVID in AA patients, because of their unique complications and the potential implications for AA therapy, including the use of calcineurin inhibitors and timing and donor selection for hematopoietic stem cell transplantation.

CVID is the most common primary immunodeficiency caused by a failure of B-cell differentiation into functional plasma cells leading to immunoglobulin deficiency and recurrent sinopulmonary infections. Some CVID patients also have autoimmune and inflammatory manifestations (Table 1; Patuzzo et al. 2016; Lorenzini et al. 2020). In up to 20% of CVID patients, a genetic cause can be identified. Monoallelic loss-of-function mutations in \textit{NFKB1} are found in 4% of CVID patients and are the most common cause of familial CVID (Kaustio et al. 2017; Tuijnenburg et al. 2018; Lorenzini et al. 2020). NF-\kappa B proteins are a family of five transcription factors (p50/p105, p52/p100, RelA, RelB, and c-Rel) characterized by a conserved DNA-binding domain (Rel homology domain). Dimers of NF-\kappa B proteins direct transcriptional regulation of genes involved in various cellular processes including immune and inflammatory responses (Karin and Lin 2002; Lougaris et al. 2017). Intact NF-\kappa B signaling contributes to proper B-cell maturation, survival, differentiation, and T-cell-independent antibody class switching (Vallabhapurapu and Karin 2009; Gerondakis and Siebenlist 2010; Kaileh and Sen 2012).

Although immune-mediated bone marrow failure has not been previously reported in CVID patients, the association of \textit{NFKB1}-mutated CVID with other autoimmune disorders suggests that the cooccurrence of AA and CVID in our patient was not coincidental. In fact, \textit{NFKB1} was previously found to have a critical role for maintaining a resting state of dendritic cells (DCs), induction of T-cell tolerance, and CD8+ lymphocyte cytotoxicity (Dissanayake et al. 2011). When pulsed with self-antigens, unstimulated DCs lacking \textit{NFKB1} may activate CD8+ T lymphocytes, leading to autoimmunity (Dissanayake et al. 2011). The absence of \textit{NFKB1} in resting antigen-presenting cells is associated with poor induction of T-cell tolerance and higher granzyme B expression in cytotoxic T cells, pointing to the role of dendritic cell defects in the establishment of autoimmunity in NKFB1-deficient.
Table 2. Clinical findings in autosomal dominant NFKB1 deficiency

| Clinical features                                      | Patient |
|--------------------------------------------------------|---------|
| Autosomal dominant inheritance                         | Yes     |
| Respiratory system                                     |         |
| Upper respiratory tract infections (83.0%)             | Yes     |
| Pneumonia (59.0%)                                      |         |
| Bronchiectasis (25.6%)                                 |         |
| Granulomatous lymphocytic interstitial lung disease (GLILD) (7.4%) |         |
| Gastrointestinal complications                         |         |
| Gastrointestinal infections (28.6%)                    |         |
| Autoimmune enteropathy (13.9%)                         | Yes     |
| Celiac-like disease (9.3%)                             |         |
| IBD-like disease (5.6%)                                |         |
| Diarrhea of unknown etiology (8.3%)                    |         |
| Atrophic gastritis (4.6%)                              |         |
| Liver                                                   |         |
| Hepatomegaly (24.7%)                                   |         |
| Liver disease (19.5%)                                  | Yes     |
| Malignancies (16.8%)                                   |         |
| Lymphoma (11.1%)                                       |         |
| Solid organ cancer (4.6%)                              | Yes     |
| Spleen                                                  |         |
| Splenomegaly (48.5%)                                   |         |
| Splenectomy (11.9%)                                    | Yes     |
| Bone marrow                                             |         |
| Antibody deficiency (88.9%)                             | Yes     |
| Low IgA (87.4%)                                        | Yes     |
| Low IgG (74.4%)                                        | Yes     |
| Low IgM (70.9%)                                        | Yes     |
| Cytopenia (43.9%)                                      | Yes     |
| Novel clinical features                                 |         |
| Acquired aplastic anemia                               | Yes     |
| Skin                                                    |         |
| Skin infections (37.7%)                                |         |
| Rosacea                                                 |         |
| Autoimmune (14.9%)                                     |         |
| Psoriasis                                               |         |
| Eczema                                                  |         |
| Necrotizing fasciitis                                   |         |
| Alopecia                                                |         |
| Thyroiditis (6.5%)                                     |         |
| Cardiovascular system                                  |         |
| Cardiovascular complications (17.8%)                   |         |
| Behçet disease (5.6%)                                  |         |
| Vasculitis (4.6%)                                      |         |

(Continued on next page.)
patients (Dissanayake et al. 2011). Additionally, CVID patients were previously found to have lower numbers of T regulatory cells, which may also contribute to the development of AA (Fevang et al. 2007). Further studies are needed to better evaluate the role of *NFKB1* and other genetic variants of immune regulation in the development of AA.

After the development of AA, our patient experienced rapid decline, further complicated by the difficulty in tolerating standard aplastic anemia therapy. Within days of starting therapeutic doses of cyclosporine, the patient experienced generalized failure to thrive, weight loss, hepatic dysfunction, and recurrent infections. The patient also recalled that during her previous treatment with low-dose cyclosporine, she also subjectively felt that “cyclosporine did not agree with her.” Notably, cyclosporine is a potent inhibitor of T-cell activation and has multiple cellular functions, the best known of which is inhibition of calcineurin. Intracellular calcium release and its regulation by calcineurin were also found to be critical for NF-κB activation (Frantz et al. 1994; Steffan et al. 1995; Chan et al. 2013), and treatment with calcineurin inhibitors cyclosporine and tacrolimus has been shown to suppress NF-κB signaling (Venkataraman et al. 1995; Marienfeld et al. 1997; Meyer et al. 1997; Jin et al. 2015). We suspect that the use of cyclosporine in the context of *NFKB1* haploinsufficiency may have led to enhanced toxicity as a result of further inhibition of NF-κB-dependent processes. Other CVID-related complications contributing to the poor outcome in our patient include recurrent infections, CVID enteropathy, and hepatic dysfunction.

In summary, in this report we expand the spectrum of hematologic complications of CVID to include AA and establish a novel link between genetic disorders of immune regulation and AA. Our case highlights potential challenges in managing AA in patients with CVID because of the underlying immune dysregulation, chronic complications of CVID, and what appears to be an epistatic interaction of calcineurin inhibitors in patients with genetic alterations of the NF-κB pathway. Increased recognition of immune-mediated bone marrow failure as a potential etiology of cytopenias in patients with CVID may improve outcomes by intervening at earlier stages of the disease and by anticipating potential complications. Allogeneic stem cell transplantation can be considered in selected patients; however, historical outcomes in CVID patients treated with bone marrow transplant have been poor, because of the high rates of treatment-refractory graft-versus-host disease and poor immune reconstitution leading to infectious complications (Wehr et al. 2015). Future studies are needed to determine optimal immunosuppressive therapies and transplant approaches in this difficult-to-treat patient population.

| Table 2. (Continued) |
|----------------------|
| **Clinical features** | **Patient** |
| Bone/Joints          |            |
| Osteopenia (12.9%)   |            |
| Arthritis (10.3%)    |            |
| Enthesiopathy        |            |
| Aphthous ulcerations (17.8%) | |
| Neurological complications (13.9%) | |
| Noninfectious fever (12.0%) | |
| Lymphoproliferation  |            |
| Lymphadenopathy (35.3%) | |

The summary of clinical features is adapted from Lorenzini et al. 2020.
METHODS

Patient Recruitment and Regulatory Approval
The patient was enrolled into Penn–CHOP Bone Marrow Failure cohort, a bone marrow failure registry study approved by the Institutional Review Boards of Children’s Hospital of Philadelphia and the University of Pennsylvania (IRB # 10-007569). Informed consent from the patient was obtained in accordance with the Declaration of Helsinki. The diagnosis of aplastic anemia was established using standard criteria (International Agranulocytosis and Aplastic Anemia Study 1987; Wilson et al. 2014).

Whole-Exome Sequencing
Whole-exome sequencing was performed on patient’s genomic DNA extracted from peripheral blood by paired-end massively parallel sequencing at the CLIA-approved commercial genetic testing laboratory (XomeDxPlus test, GeneDx). The exonic regions and flanking splice junctions were captured using a GeneDx proprietary system and sequenced at a mean depth of coverage of 158×, with 98.7% of the captured regions covered by at least 10 sequence reads. Reads were aligned to human genome build GRCh37/UCSC hg19 and analyzed using a custom-developed analysis tool (XomeAnalyzer, GeneDx). Capillary sequencing was used to confirm all potentially reportable variants (Fig. 2).

Hematopathology and Ancillary Studies
Bone marrow histology was evaluated by a hematopathologist prior to the study enrollment. Cytogenetic analysis was performed by standard karyotyping techniques. Analysis of somatic mutations in genes associated with hematologic malignancies was performed at the University of Pennsylvania Center for Personalized Diagnostics as previously described (Fox et al. 2016), with the following 68 genes analyzed (ABL1, ASXL1, ATM, BCOR, BCO2L1, BIRC3, BRF, CALR, CBL, CDKN2A, CEBPA, CSF1R, CSF3R, DDX3X, DNMT3A, ETV6, EZH2, FAM5C, FBXW7, FLT3, GATA2, GNAS, HNRNPK, IDH1, IDH2, IL7R, JAK2, KIT, KLHL6, KRAS, MAP2K1, MAPK1, MIR142, MPL, MYC, MYCN, MYD88, NF1, NOTCH1, NOTCH2, NPM1, NRAS, PDGFRA, PHF6, POT1, PRPF40B, PTEN, PTPN11, RAD21, RIT1, RUNX1, SETBP1, SF1, SF3A1, SF3B1, SMC1A, SRSF2, STAG2, TBL1XR1, TET2, TP53, TPMT, U2AF1, U2AF2, WT1, XPO1, ZMYM3, ZRS2). TRG gene rearrangements were analyzed by PCR-based amplification using consensus V and J primers and capillary electrophoresis at the Penn Molecular Diagnostics Laboratory.

Telomere Length Measurement and Chromosome Breakage Testing
Flow-FISH telomere length measurements were performed on the lymphocyte subsets total lymphocytes, CD45RA positive naive T cells, CD45RA negative memory T cells, and CD57 positive NK cells at the CLIA-certified clinical telomere length testing center (Repeat Diagnostics, Inc.). Chromosome breakage testing in the presence or absence of mitomycin C and diepoxybutane with appropriate controls was performed on patient’s lymphocytes at the Comprehensive Center for Fanconi Anemia.

ADDITIONAL INFORMATION

Data Deposition and Access
The patient’s NFKB1 variant NM_003998.4(NFKB1):c.702del (p.Val235fs) was deposited to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) under the accession number VCV000450428.2, variation ID: 450428. Patient consent was not granted to deposit WES data.
Ethics Statement
The patient was enrolled into the Penn–CHOP Bone Marrow Failure cohort, a bone marrow failure registry study approved by the Institutional Review Boards of Children’s Hospital of Philadelphia and the University of Pennsylvania (IRB # 10-007569). Informed consent from the patient was obtained in accordance with the Declaration of Helsinki.

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Author Contributions
T.S. and D.B. performed the clinical review, analyzed the literature, and wrote and edited the manuscript. J.J. performed genetic sequencing analysis. S.N.H. and A.B. reviewed histopathology and ancillary studies. N.L.S. performed clinical chart review and prepared laboratory data tables. All authors revised the manuscript and are in agreement with the final version of the manuscript.

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