

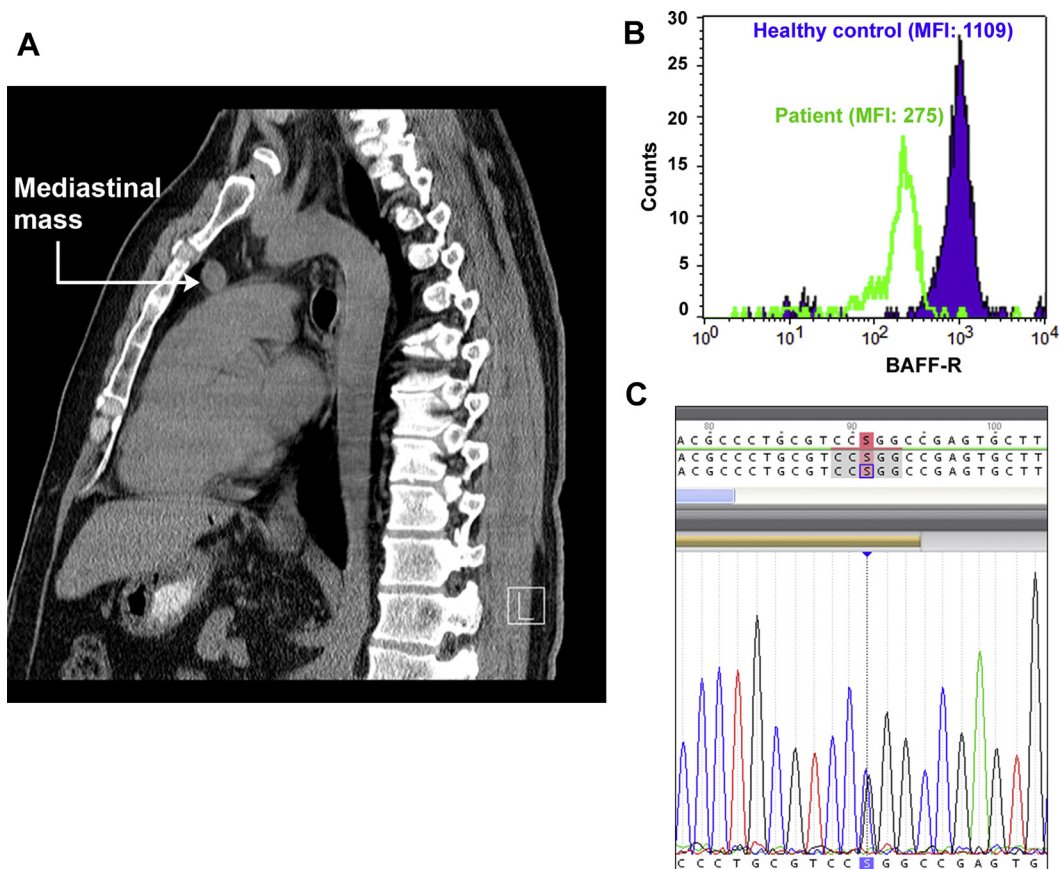


Figure 1. A, A sagittal view of a chest computed tomograph showing a small, well-circumscribed anterior mediastinal mass. B, Flow cytometric analysis of B-cell activating factor receptor (BAFF-R) expression on CD19⁺ blood B cells from the patient (green) and a healthy control (dark purple). Mean fluorescence 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).

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A new subset of common variable immune deficiency characterized by reduced C1 esterase inhibitor levels



Common variable immune deficiency (CVID) is a common form of severe antibody deficiency. CVID is characterized by infections, gastrointestinal disorders, autoimmune diseases, and increased susceptibility to malignant neoplasms.¹ Patients with CVID lack the ability to make a sufficient amount of antibodies to protect them from infections. Intravenous immunoglobulin (IVIG) is used for replacement therapy at 400 to 800 mg/kg and has been found to reduce infection rates for

all forms of primary immunodeficiency.^{2,3} IVIG is relatively safe, with headaches and fatigue being the most common adverse events (AEs). More severe complications, such as aseptic meningitis, are rare. Similarly, the mechanism that results in undesirable AEs is also not clear. The current standard of care for patients who cannot tolerate IVIG is a switch to subcutaneous immunoglobulin (SCIG), which reduces AEs. It is still unclear the reasons for reduced AEs with the SCIG delivery.

Immunoglobulins (IgG subclasses 1, 2, and 3 and IgM) interact with complement and bind to or cause the direct

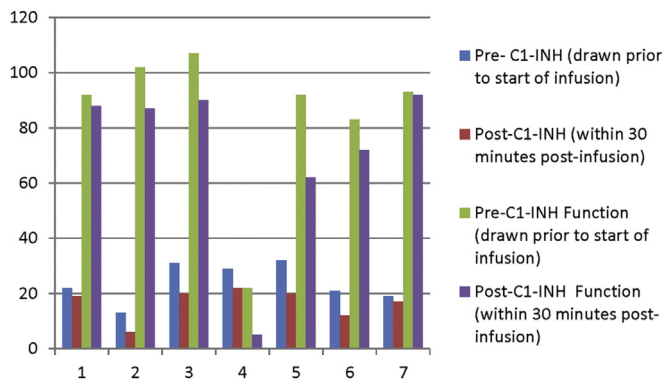


Figure 1. C1-inhibitor (C1-INH) functional assay results reported as the percentage of mean normal activity. Quantitative assays report C1-INH concentration in milligrams per deciliter.

killing of a microbe or interact with phagocytes to cause microbial ingestion and killing by phagocytic cells. Complement proteins form a trio of intersecting enzyme cascades that result in a number of protective mechanisms that bind to foreign surfaces and thus fight viruses, bacteria, and other foreign substances.³ Once the complement cascade has been initiated, there are mechanisms that inhibit or slow the process reaction at various steps. Without these checks in the system, uncontrolled complement activation can lead to alteration of blood flow, inflammation, and tissue lesions. C1 esterase inhibitor (C1-INH) is the major inhibitor of the classic pathway.^{4,5} In addition to blocking activity of C1r and C1s, C1-INH has several noncomplement target proteases, including factor XIIIa and kallikrein of the kinin pathway, plasmin, and mannose-associated serine proteases 1 and 3 of the lectin pathway. C1-INH belongs to the family of serpins. Recent studies suggest some anti-inflammatory function for this molecule, possibly explaining the effects of C1-INH in diseases other than hereditary angioedema.⁶ Acquired deficiency of C1-INH can accompany activation of complement with consumption of C1-INH and hyperactivation of the classic pathway. This relationship has also been suggested with autoimmune (autoantibodies against the inhibitor) or lymphoproliferative diseases.⁶

C1-INH deficiency has been recently linked to antibody deficiency.⁷ Moreover, our preliminary research suggests that C1-INH deficiency may be part of immune deficiency. On the basis of observations, we ran additional testing of C1-INH levels (protein levels and functional enzymatic activity) in patients newly diagnosed as having CVID for baseline levels. We tested a total of 80 patients; 30 of these patients had low levels of C1-INH protein, varying from 6 to 20 mg/dL (mean, 16.7 mg/dL; reference range, 21–39 mg/dL), and/or reduced enzyme function, ranging from 11% to 65% (mean [SD], 37.3% [12%], with 67% of mean normal enzymatic function being the lower limit of what is considered normal enzyme activity). Of this subset of the CVID population, 24 were female (7 patients were 13–32 years old, 12 patients were 33–50 years old, and 5 patients were 51–65 years old) and 6 were male (3 patients were 10–20 years old and 3 patients were 60–70 years old). Of note, the C4 complement levels were within the reference ranges.

The clinical presentations of the patients with CVID and low C1-INH levels were extreme fatigue in 90% and an autoimmune presentation in 80% (50% gastrointestinal disorders, 40% arthralgia, 20% neuropathy, 30% migraine, and 10% mild cognitive changes).

As we began to explore C1-INH levels, we also noted that IVIG therapy can downregulate C1-INH or C1-INH function levels, and this downregulation was associated with increased AEs, such as headache (80%) and increased fatigue (60%). Sixteen patients with CVID were tested before and after infusion because of infusion-related AEs. These patients were receiving different commercially available, Food and Drug Administration–approved IVIG products, so no correlation was noted for a particular IVIG product. In Figure 1, we present laboratory values for 7 patients that reveal a change in C1-INH and C1-INH function levels before and after IVIG infusion (patients 4 and 5 had aseptic meningitis after infusion).

We therefore propose that, in a subset of patients, CVID is characterized by lower serum C1-INH protein concentration and/or enzymatic C1-INH function. These patients often had symptoms of limb edema, abdominal swelling, and edema or facial edema similar to those experienced by patient with hereditary angioedema.⁸ These patients also experienced AEs, such as headache and fatigue. Low C1-INH or C1-INH function may imply that these patients are more vulnerable to AEs of IVIG therapy. As a possible mechanism for AEs, we hypothesize that the infusion of IgGs may trigger consumption of complement proteins and of C1-INH, precipitating inflammatory reactions, including aseptic meningitis. These preliminary observations raise further questions that need to be studied, including the following: (1) Does C1-INH play a role in autoimmune diseases and cancer? (2) Should we test C1-INH levels in CVID before IVIG treatment to determine the use of a 10%, 5%, or subcutaneous product? and (3) Does the subcutaneous delivery have a different mechanism in relation to C1-INH? This may suggest a different mechanism for SCIG compared with IVIG in regard to complement activation and indirectly to AEs. We propose further studies to clarify our hypothesis.

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