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# Inflammatory and autoimmune complications of common variable immune deficiency

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**Abstract**

Common variable immune deficiency (CVID) is associated with autoimmune and inflammatory complications in addition to recurrent infections. The most common conditions are idiopathic thrombocytopenia purpura, autoimmune hemolytic anemia, sarcoid-like granulomatous disease and gastrointestinal inflammation. IVIG administration reduces the frequency of infections, but does not always prevent autoimmunity or inflammation. TNF antagonists and anti-CD20 immunomodulators have shown some efficacy in CVID in a few patients; further controlled studies are needed to determine the best management of these conditions in the setting of immunodeficiency.


*Keywords:* Common variable immune deficiency; Autoimmunity; Idiopathic thrombocytopenia purpura; Hemolytic anemia

Autoimmune and inflammatory diseases have long been recognized and reported in patients with primary immunodeficiency. Common variable immune deficiency, IgA deficiency, hyper IgM syndrome, complement defects, autoimmune lymphoproliferative syndrome, mucocutaneous candidiasis and Wiskott–Aldrich syndrome are the primary immune defects most closely associated with autoimmunity [1]. The autoimmunity may be due to the lack of immunologic regulatory mechanisms or ineffective clearance of antigens [1–3].

## 1. Case example

Patient Y presented with encephalitis at age 10 and by age 18 had pulmonary lymphocytic infiltrates with poorly formed pulmonary granulomas, requiring corticosteroids for control. Two years later, respiratory failure and splenomegaly led to the diagnosis of CVID with low immunoglobulin levels (IgG 295 mg/dL, IgA < 7 mg/dL, IgM 30 mg/dL). Intravenous immunoglobulins and prophylactic antibiotics were added to her therapy. Despite this treatment, at age 22, continuous oxygen therapy was required for increasing respiratory failure due to progressive pulmonary infiltrates. Review of a pulmonary biopsy showed granulomata and T cells. Cyclosporine (100 mg a day) was added to her prednisone (30 mg a day).

At age 26, Patient Y presented with sudden onset of jaundice and fatigue to the emergency department. She had not been feeling well for three days, but had no specific complaints suggestive of a localized infection. Her hemoglobin level was 4.6 mg/dL; Comb's test was positive. Two weeks prior her hemoglobin was 13.4 mg/dL during a routine outpatient visit. Supportive

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therapy for acute hemolytic anemia included red cell transfusions and high dose corticosteroids. She was admitted to the ICU with continued massive hemolysis (hemoglobin dropping as low as 1 mg/dL). Despite maximal resuscitative efforts, respiratory failure, renal failure and acidosis soon followed. She expired from autoimmune hemolytic anemia the following morning, less than 24 h after admission.

## 2. Common variable immune deficiency (CVID)

Serum immuglobulin levels IgG and IgA and/or IgM in CVID are reduced more than 2 standard deviations below normal values and specific antibody responses to infection or vaccination challenge are absent or impaired. Reduced numbers or function of T and B cells as well as cytokine and dendritic cell defects are variably present [4–6].

Pneumonia and sinusitis are the most common infectious presentations of CVID. Others include meningitis, encephalitis, otitis media, osteomyelitis, and infectious diarrhea. The infections can be recurrent and life threatening; it is preferable to identify the immune defect and initiate treatment prior to the onset of significant complications such as chronic lung disease. Patients with CVID are also at higher risk of malignancy, especially non-Hodgkins lymphoma.

## 3. Autoimmune disease incidence and manifestations in CVID

Approximately 23% of CVID patients develop autoimmune disease (Table 1) [7]. The most frequent are idiopathic thrombocytopenia purpura (ITP) and autoimmune hemolytic anemia (AHA) [1,7]. The underlying etiology of autoimmune disease in CVID is unknown. B cells may undergo abnormal somatic hypermutation or there may be a failure to remove self-reactive B cells due to defective receptor editing [8,9]. Autoimmune conditions associated with CVID are not limited to those mediated by autoantibody, but encompass the T cell mediated diseases such as rheumatoid arthritis and pernicious anemia. There may also be innate immunity defects leading to altered handling of antigens [10].

Table 1
Autoimmune conditions reported in patients with CVID

| | |
|---|---|
| Idiopathic thrombocytopenia purpura | Nephrotic syndrome |
| Hemotytic anemia | Systemic lupus erythematosus |
| Rheumatoid arthritis | Vasculitis |
| Juvenile rheumatoid arthritis | Dermatomyositis |
| Sicca syndrome | Sjogren's syndrome |
| Primary biliary cirrhosis | Guillain–Barre |
| Alopecia | Hyperthyroidism |
| Pernicious anemia | Autoimmune neutropenia |

A variety of autoimmune complications have been reported in patients with CVID [1,7,13,25–27]. It is not possible to predict which patients will develop autoimmune or inflammatory complications.

## 4. Inflammatory and granulomatous disease in CVID

About half of patients experience chronic diarrhea with malabsorption and have histological findings suggestive of inflammatory bowel disease [7,11]. The most common abnormality is nodular lymphoid hyperplasia, though there may be significant lymphoid infiltration into the intestinal lamina propria contributing to symptoms [12].

8–20% of CVID patients develop granulomatous disease similar to sarcoid, a condition also associated with shorter survival and a higher incidence of autoimmunity [13,14]. The lung is a common site of granulomatous disease though it may not be diagnosed until patients have significant respiratory symptoms. Lymphoid interstitial pneumonitis can lead to significant lung pathology despite antibiotics and IVIG treatment [15].

## 5. Treatment of CVID

Replacement of IgG immunoglobulin with intravenous Immunoglobulin G (IVIG) significantly reduces the incidence of pneumonia [16], although patients may continue to experience recurrent sinusitis and gastrointestinal inflammation. Infections should be aggressively treated with antibiotics and some require prophylactic antibiotics.

Treatment for infections does not eliminate the inflammatory sequelae associated with CVID, suggesting these complications are not secondary to infection [17]. However replacement dosing of IVIG does appear to reduce the frequency of recurrent ITP and HA [18]. Corticosteroids are often first line therapy for the autoimmune and inflammatory complications, but chronic treatment is associated with significant complications and should be avoided [7]. Hydroxychloroquine may have benefit through reduction of antigen presentation and inhibition of TNF release; though less effective, it can be a relatively safe alternative or used in addition to low dose steroids. T cell mediated complications may be treated by cyclosporine, mycophenolate mofitil or methotrexate with vigilance for opportunistic infections and malignancy [7].

Patients with CVID associated granulomatous disease appear to have increased levels of TNF; this has been hypothesized to contribute to the development of the granuloma [19–21]. A TNF antagonist promoted improvement in alopecia associated with cutaneous granulomas, diarrhea, and joint pain in a patient with CVID [22]. In addition, case reports suggest there can be successful treatment of the antibody mediated autoimmune disease hemolytic anemia by rituximab (anti-CD20 monoclonal antibody) in the setting of immunodeficiency [23] including CVID [24].

There have not been systematic trials of these agents to determine the optimal regiment for CVID associated autoimmunity and inflammation. If successful, these treatments may reduce morbidity for CVID patients.

## 6. Summary

Patients with CVID have an 8% to 25% incidence of autoimmune and inflammatory diseases. While IVIG may prevent reoccurrences of pneumonia, ITP, and HA, it does not ameliorate granulomatous disease, or in most cases, improve inflammatory gastrointestinal conditions. While low dose corticosteroids are often helpful in controlling these conditions, all immunosuppressive agents must be used with caution in CVID. Cyclosporine has been used in some cases of chronic lung disease, especially if T cell infiltrates are documented; hydroxychloroquine may be useful if monocytes or macrophages are prominent. TNF antagonists and anti-CD20 in CVID have been used in individual cases of granulomatous disease or autoimmunity, respectively; the best use of these therapies has not yet been clarified.

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**Take-home messages**

- CVID is associated with autoimmune and inflammatory disease.
- Patients with recurrent ITP or HA and granulamatous disease should be investigated for CVID.
- Control of infections in immunodeficiency may not control autoimmune and inflammatory complications.
- In the future, T cell immunosuppressives, hydroxychloroquine, TNF antagonists and anti-CD20 may be used for the treatment of inflammatory and autoimmune complications of CVID.

## References

[1] Cunningham-Rundles C. Hematologic complications of primary immune deficiencies. Blood Rev 2002;16(1):61–4.
[2] Etzioni A. Immune deficiency and autoimmunity. Autoimmun Rev 2003;2(6):364–9.
[3] Giannouli S, Anagnostou D, Soliotis F, Voulgarelis M. Autoimmune manifestations in common variable immunodeficiency. Clin Rheumatol 2004;23(5):449–52.
[4] Kokron CM, Errante PR, Barros MT, Baracho GV, Camargo MM, Kalil J, et al. Clinical and laboratory aspects of common variable immunodeficiency. An Acad Bras Cienc 2004;76(4):707–26.
[5] Cunningham-Rundles C. Common variable immunodeficiency. Curr Allergy Asthma Rep 2001;1(5):421–9.
[6] Cunningham-Rundles C. Immune deficiency: office evaluation and treatment. Allergy Asthma Proc 2003;24(6):409–15.
[7] Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999;92(1):34–48.
[8] Levy Y, Gupta N, Le Deist F, Garcia C, Fischer A, Weill JC, et al. Defect in IgV gene somatic hypermutation in common variable immuno-deficiency syndrome. Proc Natl Acad Sci U S A 1998;95(22):13135–40.
[9] Meffre E, Davis E, Schiff C, Cunningham-Rundles C, Ivashkiv LB, Staudt LM, et al. Circulating human B cells that express surrogate light chains and edited receptors. Nat Immunol 2000;1(3):207–13.
[10] Mullighan, Marshall, Welsh. Mannose binding lectin polymorphisms are associated with early age of disease onset and autoimmunity in common variable immunodeficiency. Scand J Immunol 2000;51(2):111–22.
[11] Cunningham-Rundles C. Clinical and immunologic analyses of 103 patients with common variable immunodeficiency. J Clin Immunol 1989;9(1):22–33.
[12] Hermans PE, Huizenga KA, Hoffman HN, Brown Jr AL, Markowitz H. Dysgammaglobulinemia associated with nodular lymphoid hyperplasia of the small intestine. Am J Med 1966;40(1):78–89.
[13] Mechanic LJ, Dikman S, Cunningham-Rundles C. Granulomatous disease in common variable immunodeficiency. Ann Intern Med 1997;127(8 Pt 1):613–7.
[14] Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol 2004;114(2):415–21.
[15] Davies CWH, Juniper MC, Gray W, Gleeson FV, Chapel HM, Davies RJO. Lymphoid interstitial pneumonitis associated with common variable hypogammaglobulinaemia treated with cyclosporin A. Thorax 2000;55(1):88–90.
[16] Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J Allergy Clin Immunol 2002;109(6):1001–4.
[17] Sewell, North, Cambronero, Webster, Farrant. In vivo modulation of cytokine synthesis by intravenous immunoglobulin. Clin Exp Immunol 1999;116(3):509–15.
[18] Wang J, Cunningham-Rundles C. Treatment and outcome of autoimmune hematologic disease in common variable immunodeficiency (CVID). J Autoimmun 2005;25(1):57–62.
[19] Mullighan C, Fanning G, Chapel H, Welsh K. TNF and lymphotoxin-alpha polymorphisms associated with common variable

immunodeficiency: role in the pathogenesis of granulomatous disease. J Immunol 1997;159(12):6236–41.
[20] North, Webster, Farrant. Primary defect in CD8+ lymphocytes in the antibody deficiency disease (common variable immunodeficiency): abnormalities in intracellular production of interferon-gamma (IFN-gamma) in CD28+('cytotoxic') and CD28-('suppressor') CD8+ subsets. Clin Exp Immunol 1998;111(1): 70–5.
[21] Aukrust P, Lien E, Kristoffersen A, Muller F, Haug C, Espevik T, et al. Persistent activation of the tumor necrosis factor system in a subgroup of patients with common variable immunodeficiency-possible immunologic and clinical consequences. Blood 1996;87(2):674–81.
[22] Smith KJ, Skelton H. Common variable immunodeficiency treated with a recombinant human IgG, tumour necrosis factor-alpha receptor fusion protein. Br J Dermatol 2001;144(3): 597–600.
[23] Bonduel M, Zelazko M, Figueroa C, Magaldi G, Rossi J, Pozo AD. Successful treatment of autoimmune hemolytic anemia with rituximab in a child with severe combined immunodeficiency following nonidentical T-cell-depleted bone marrow transplantation. Bone Marrow Transplant 2005;35(8):819–21.
[24] Wakim M, Shah A, Arndt PA, Garratty G, Weinberg K, Hofstra T, et al. Successful anti-CD20 monoclonal antibody treatment of severe autoimmune hemolytic anemia due to warm reactive IgM autoantibody in a child with common variable immunodeficiency. Am J Hematol 2004;76(2):152–5.
[25] Conley ME, Park CL, Douglas SD. Childhood common variable immunodeficiency with autoimmune disease. J Pediatr 1986; 108(6):915–22.
[26] Ballow M. Primary immunodeficiency disorders: antibody deficiency. J Allergy Clin Immunol 2002;109(4):581–91.
[27] Cunningham-Rundles C. Clinical and immunologic studies of common variable immunodeficiency. Curr Opin Pediatr 1994; 6(6):676–81.

### *Susceptibility to thyroid disorders in hepatitis C.*

Autoimmune thyroid disorders (AITDs) are reported, especially during interferon treatment, in chronic HCV infection, in which non-organ-specific autoantibodies (NOSAs) are common. Muratori L. et al. (Clin Gastroenterol & Hepatol 2005;3:595–603) evaluated the possibility that seropositivity for NOSA is associated with susceptibility to AITDs. The authors evaluated thyroid function and antithyroglobulin and antithyroperoxidase antibodies in 348 Italian patients with chronic hepatitis C (34% NOSA-positive), 196 patients (33% NOSA-positive) of whom received interferon treatment. At baseline, thyroid disorders were significantly more frequent in liver/kidney microsomal antibody type 1 (LKM1)-positive patients (29% vs 9%, $p < 0.005$). Similarly, on interferon therapy de novo autoimmune thyroid markers and/or symptomatic thyroid disorders appeared more often in LKM1-positive patients (50% vs 3%, $p < 0.001$). Cross-reactivity to all 7 linear epitopes encoding homologous amino acid sequences shared by the HCV polyprotein, CYP2D6 (the LKM1 autoantigen), and thyroperoxidase was detected in 86% LKM1-positive HCV patients with clinical thyroid disorders. Thus, patients receiving interferon therapy for hepatitis C and seropositive for LKM1 are susceptible to develop AITDs, in association with treatment. Molecular mimicry and epitope spreading are potential pathogenic mechanisms.

### *Serological correlations with nephritis in systemic lupus erythematosus.*

Autoantibodies have long been thought to participate in the pathogenesis of lupus nephritis. In this regard, antibodies to dsDNA and ribosomal P protein have been studied the most intensively. In this study, Reichlin M. (Clin Immunol 2005;117:12–4) report on a new specificity, antibodies to lipoprotein lipase (LPL) that is strongly associated with lupus nephritis and has a powerful synergistic effect with anti-ribosomal P antibodies in its association with nephritis. The recognition of anti-LPL antibodies and their synergy with anti-P antibodies are discussed in terms of the pathogenesis of lupus nephritis.