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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].