Etanercept treatment of cutaneous granulomas in common variable immunodeficiency

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Common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by hypogammaglobulinemia, poor antibody responses, and recurrent bacterial infections, usually of the sinorespiratory tract. A not uncommon complication is granuloma of the lungs, spleen, liver, and/or skin. We report the case of an 18-year-old boy with CVID and chronic granulomas of the left arm (since 13 years of age) refractory to treatment with antibiotics, intravenous immunoglobulin, antifungal agents, systemic and intralesional steroids, IFN-γ, cyclosporine, methotrexate, hydroxychloroquine, localized radiation therapy, and surgical excision. The lesions improved after treatment with the systemic administration of the TNF-α inhibitor etanercept for 1 year. Etanercept prevents soluble TNF from binding to its cell membrane receptor, leading to inhibition of its inflammatory cascade. We recommend further trials of etanercept in patients with CVID with noninfectious recalcitrant granulomas.
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Key words: *Common variable immunodeficiency, granuloma, TNF-α inhibitors, etanercept*

Abbreviations used
CVID: Common variable immunodeficiency
IVIG: Intravenous immunoglobulin

Common variable immunodeficiency (CVID) is the most common severe primary immunodeficiency, affecting 1:50,000 to 1:200,000 individuals.[1] The usual age of onset is 20 to 30 years,[2] but children can present as early as 2 years of age. Most patients with CVID have progressive hypogammaglobulinemia involving all immunoglobulin classes, poor or absent antibody responses, and recurrent bacterial infections, usually of the sinorespiratory tract. Patients with CVID might have associated gastrointestinal, autoimmune, lymphoproliferative, malignant, and granulomatous complications.[3] About 5% to 10% of patients with CVID have sarcoid-like granulomas.[4] These granulomas can involve the lungs, spleen, liver, and/or skin. Many of the latter patients have associated splenomegaly, T-cell dysfunction, and increased serum TNF-α levels.[5]

We describe a boy given a diagnosis of CVID at 7 years of age who had recurrent cutaneous granulomas of the left arm at age 13 years. The lesions were refractory to antibiotics, antifungal agents, systemic and intralesional steroids, IFN-γ, cyclosporine, methotrexate, hydroxychloroquine, localized radiation therapy, and surgical excision administered over 5 years. The lesions improved markedly after injections of the TNF-α inhibitor etanercept given for 12 months. This is the second published report of etanercept in the treatment of the cutaneous granulomas of CVID.

CASE REPORT

The patient presented at age 7 years with recurrent sinus infections refractory to antibiotics and surgery and persistently low IgG and IgM levels. At that time, his IgG level was 424 mg/dL (normal range for age, 560-1400 mg/dL), and his IgM level was 42 mg/dL (normal range for age, 50-211 mg/dL). Diagnostic workup included normal-appearing cilia on electron microscopy of the turbinates, a normal sweat test result, and a negative HIV serology. T- and B-cell subsets were normal, including normal CD19 cells. He showed adequate postvaccination antibody responses to tetanus toxoid, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. Monthly intravenous immunoglobulin (IVIG) was started at age 10 years after the patient continued to have persistent sinus infections despite being given prophylactic antibiotics and IgG levels did not normalize. IgG troughs increased from 480 mg/dL to the 600 to 700 mg/dL range during therapy, and symptoms improved to the point that he did not require continuous antibiotics for treatment of sinusitis. After 3 years of monthly IVIG, the patient chose to go off therapy and has not resumed monthly infusions.

At age 13 years, he presented with splenomegaly and multiple reddish-purple, nodular, granulomatous lesions

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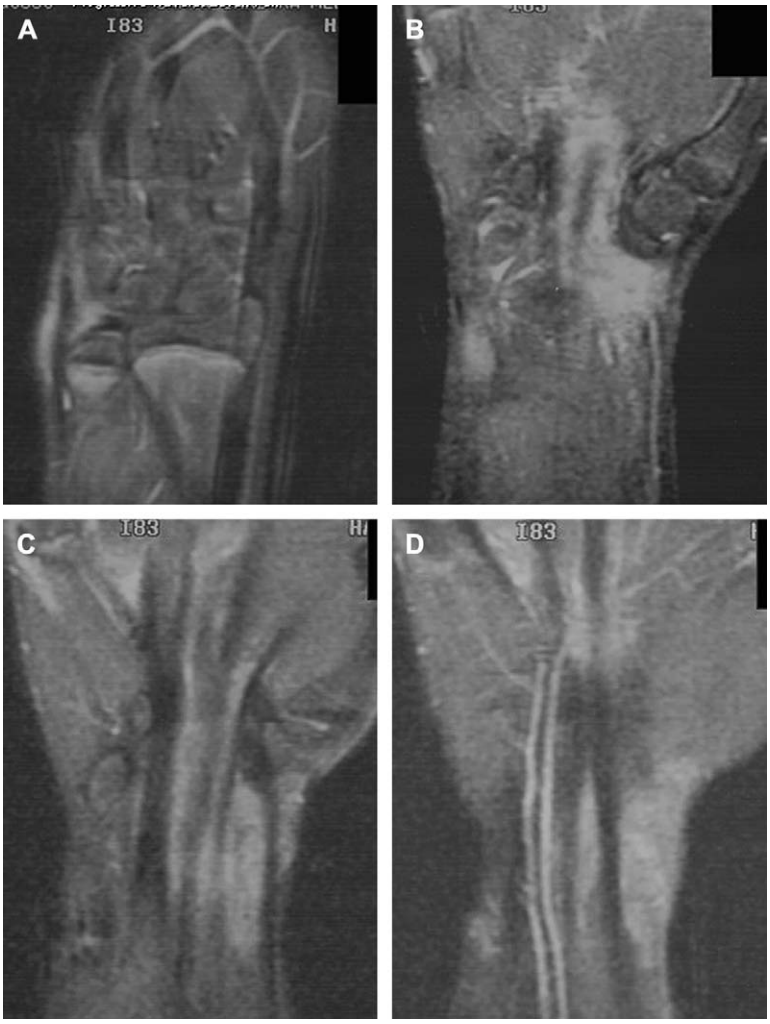

FIG 1. Computed tomographic scan with coronal views (short tau inversion recovery [STIR] time to repetition [TR] 4000, time to echo [TE] 25 ms) of patient's distal left upper extremity. High signal intensity shows infiltrating soft tissue mass surrounding extensor carpi ulnaris **(A)** and flexor **(B-D)** tendons. The mass is seen insinuating itself between the tendon sheath, distal radius, scaphoid, and deep flexor tendons in Fig 1, *B*, *C*, and *D*.

of the left arm, which involved the upper arm, volar forearm, and index finger. The lesions were painful and resulted in a markedly decreased range of motion of the wrist, elbow, and affected finger.

Laboratory studies at this time included low total lymphocyte counts at 600 cells/μL (normal range, 1000-3500 cells/μL) and decreased CD4 counts at 246 cells/μL (normal range, 440-1600 cells/μL), CD3 counts at 372 cells/μL (normal range, 740-2400 cells/μL), CD19 counts at 152 cells/μL (normal range, 90-640 cells/μL), and CD8 counts at 96 cells/μL (normal range, 170-940 cells/μL). Immunoglobulin levels were low, with IgA levels of 8 mg/dL (normal range, 32-468 mg/dL), IgM levels of 10 mg/dL (normal range, 32-248 mg/dL), and IgG levels of 370 mg/dL (normal range, 560-1700 mg/dL). IgG subsets showed low IgG_1 levels at 237 mg/dL (normal range, 350-965 mg/dL), IgG_2 levels at 35 mg/dL (normal range, 81-500 mg/dL), and IgG_4 levels at less than 0.2 mg/dL (normal range, 7-530 mg/dL). IgG_3 levels were normal at 20 mg/dL (normal range, 16-138 mg/dL). There was no antibody response to pneumococcus polysaccharide vaccination, but he continued to show adequate antibody response to tetanus toxoid. Lymphoproliferative assay to *Candida* species was absent and to PHA was low. The angiotensin-converting enzyme level was mildly increased at 118 U/L (normal range, 8-52 U/L).

Biopsy of one of the lesions revealed an infiltrating noncaseating granuloma, with stains and cultures negative for acid-fast organisms and other bacteria. Skin biopsy revealed a dermal infiltrate composed mainly of T cells ($CD3^+$) and macrophages ($CD68^+$). Antibodies to *Coccidioides immitis*, *Bartonella henselae*, and *Sporothrix schenckii* were negative. A magnetic resonance imaging scan of the left wrist and arm showed a diffuse soft tissue lesion infiltrating the tendon sheaths.

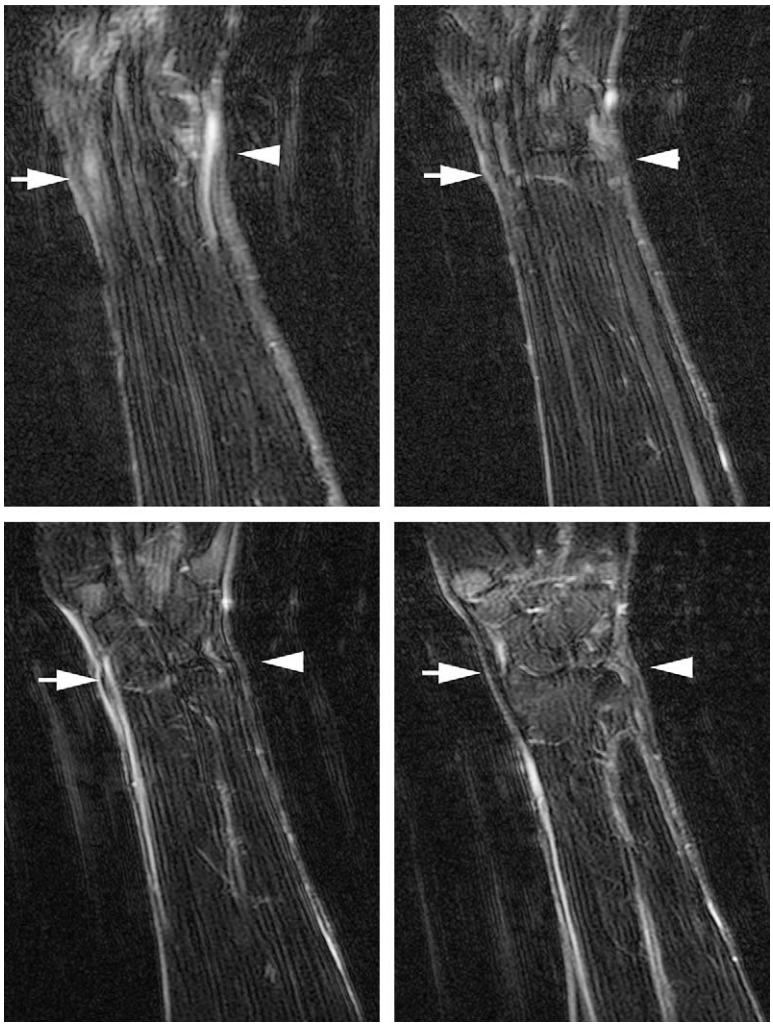

FIG 2. Magnetic resonance imaging scan with coronal views (T2 fat suppression) of the patient's distal left upper extremity 12 months after treatment with etanercept. There is decreased signal intensity of the flexor carpi radialis *(arrow)* and extensor carpi ulnaris *(arrowhead)* tendons.

The patient underwent extensive surgical excision of the mass and median nerve decompression, but it continued to recur. Ten months after surgery, computed tomography of the left wrist again showed infiltrating soft tissue surrounding the extensor carpi ulnaris and flexor carpi radialis tendons (Fig 1). Other therapeutic interventions, including antibiotics (trimethoprim-sulfamethoxazole, cephalosporin, penicillin derivatives, macrolides, and metronidazole), antifungal agents, systemic and intralesional steroids, IFN-γ, cyclosporine, methotrexate, hydroxychloroquine, and localized radiation therapy were without therapeutic benefit.

At 18 years of age, he was started on etanercept at 25 mg subcutaneously twice a week. After 1 year of treatment, the patient had significant clinical improvement, with improved range of motion in the fingers. Sequential magnetic resonance imaging studies of the arm demonstrated a notable reduction in size and severity of the mass lesions (Fig 2). There was less displacement of the flexor carpi radialis tendon and less tissue between the volar surface of the distal radius and the flexor carpi radialis tendons.

The patient chose to stop regular etanercept injections after the initial year of treatment. During the past 3 years, patient compliance has been poor, with intermittent injections of etanercept, but his cutaneous granulomas have remained stable in size. Splenic size is still enlarged. He has not resumed IVIG therapy, and he has not had any major infections requiring antibiotics or hospitalizations.

DISCUSSION

The effectiveness of etanercept in our patient is similar to the results reported by Smith and Skelton in 2001.[6] They reported that etanercept markedly decreased the

size of a noncaseating epithelioid scalp granuloma in a 21-year-old man with CVID. Acid-fast, bacterial, and fungal stains were negative. After 1 year of treatment, the patient continued to do clinically well, with few infections and only mild hair thinning in areas of previous scalp involvement.

Granulomas can occur in other immune deficiencies, including chronic granulomatous disease, ataxia-telangiectasia, severe combined immune deficiency, and X-linked agammaglobulinemia.[7] About 5% to 10% of patients with CVID have granulomas that mimic sarcoidosis.[4] Individuals with sarcoidosis have noncaseating epithelial granulomas, usually associated with depressed cellular immunity, T_H cell infiltrate of affected organs, and hypergammaglobulinemia.[8] By contrast, patients with CVID have hypogammaglobulinemia and granulomas that can be both caseating and noncaseating.[9] Necrobiotic and tuberculoid granulomas have also been described in patients with CVID.[10]

The granulomas of patients with CVID usually affect the lymph nodes, spleen, liver, and gastrointestinal tract, but cutaneous granulomas in CVID are not uncommon. Krupnick et al[11] reviewed 15 patients with cutaneous granulomas and CVID. The age when cutaneous granulomas developed ranged from 2 to 77 years (mean, 33 years). Most lesions were located on the extremities, but the face and buttocks were sometimes involved. Lesions were variously described as erythematous, papular, plaque-like, indurated, and/or scaly. Biopsy results included noncaseating (n = 9) and caseating (n = 2) granulomas. Cultures in all cases were negative. Treatment included both local (1 patient) and systemic (10 patients) corticosteroids, IL-2 (1 patient), cyclosporine (1 patient), and IVIG (1 patient). Few cases had complete resolution.

The pathogenesis of these granulomas is poorly understood. One possibility is a response to an unrecognized infectious agent. Mrusek et al[12] reported the case of a 12-year-old girl who had granulomatous lymphoproliferation and hypogammaglobulinemia in association with increased *Toxoplasma* species antibody titers. However, most affected patients, as in our patient, have had extensive but unsuccessful searches for infectious causes. O'Connor and Fitzgerald[13] suggest that granulomas are secondary to altered cell-mediated and humoral immune responses, resulting in excessive or abnormal cytokine release. Mechanic et al[14] found that 16 of 17 patients with CVID granulomas had moderately to severely abnormal proliferative responses to mitogens or antigens.

Wright et al[15] described 14 of 38 patients with CVID who had low CD4/CD8 ratios caused by increased CD8 cells; of this subgroup, 71% had associated splenomegaly, and 42% had poor delayed cutaneous hypersensitivity responses. Although they did not describe the location, they also noted that 4 of the 14 individuals had granulomas. Aukrust et al[5] described a similar subgroup of 11 patients with CVID who had decreased CD4 cells and splenomegaly and found them to have higher mean serum levels of TNF-α compared with 20 control subjects or 13 patients with CVID who did not have the subgroup characteristics. There was no mention of granulomas in their discussion.

TNF-α is a key inflammatory, immunoregulatory, and proproliferative cytokine produced mainly by activated monocytes and macrophages. Mullighan et al[16] found that patients with CVID with granuloma, splenomegaly, and T- and B-cell lymphopenia were strongly associated with the uncommon *TNF* +488A allele ($P = .0005$). Persistent activation of the TNF system might lead to immunosuppressive effects on T and B lymphocytes,[5] leading to increased granuloma formation. We propose that treatments targeting TNF in patients with CVID might ameliorate noninfectious, immune-mediated granulomatous complications.

Etanercept competitively binds TNF to prevent its binding to its cell-surface receptor, present on most cell types, thus inhibiting initiation of the inflammatory cascade. Etanercept, like the mAb infliximab, is licensed for the treatment of diseases associated with increased TNF-α levels, including rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Etanercept has also been successfully used in refractory uveitis,[17] mucocutaneous manifestations of Behcet disease,[18] pemphigus vulgaris,[19] and silicone granuloma.[20] Our patient was treated with the standard adult dosage of 25 mg subcutaneously twice a week, with significant clinical improvement after 1 year of treatment. His low T cells and impaired lymphoproliferative responses suggest that he fell into the subgroup with increased levels of TNF-α.

Side effects of etanercept treatment are rare (<1%) and include headache, injection site reaction, respiratory tract infection, positive autoantibodies (including lupus autoantibodies), and lupus nephritis.[21] Patients and experimental animals receiving TNF-blocking agents might be susceptible to tuberculosis reactivation because of their inability to form a granulomatous reaction that limits mycobacterial dissemination; murine models of chronic tuberculosis show that TNF-α neutralization can lead to fatal reactivation of tuberculosis.[22] However, it is unclear whether etanercept therapy increases the risk of tuberculosis.[23] We recommend a purified protein derivative skin test, chest radiograph, or both to rule out tuberculosis infection before starting etanercept.

Infliximab is another drug that also targets TNF-α; it is an mAb against TNF-α and has been used in the treatment of granulomatous disease in patients with CVID. Hatab and Ballas[24] reported successful treatment of caseating granulomatous lymphadenopathy in a 33-year-old man after treatment with corticosteroids and IVIG failed. Thatayatikom et al[25] described a 22-year-old man who had complete resolution of lung and liver granulomas after 9 months of infliximab treatment and remained free of granulomatous disease after 18 months of follow-up.

Our use of etanercept in treating the refractory cutaneous granulomas of patients with CVID further suggests that CVID granulomas result from immune dysregulation with abnormal TNF synthesis. This experience suggests the cautious use of etanercept and other TNF agents in CVID granulomas with the caveat that an infectious disorder has been excluded.

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