

Caseating granulomatous disease in common variable immunodeficiency treated with infliximab

To the Editor:

Common variable immunodeficiency (CVID) is a primary immune deficiency disorder characterized by hypogammaglobulinemia, antibody deficiency, and recurrent infections. Although the underlying cause remains unknown, it is now clear that CVID represents a heterogeneous group of disorders with variable phenotypic defects including failure of B-cell differentiation, impaired immunoglobulin secretion, and T-cell and cytokine abnormalities.¹ Noncaseating granulomas occur in 5.4% to 10% of patients with CVID.^{1,2} Caseating granulomas, on the other hand, are rare and have been described in only a few patients with CVID.^{3,4} Here we report a patient with caseating granulomas, for which no infectious etiology could be identified, who was successfully treated with infliximab.

JB is a 33-year-old white male, diagnosed with CVID at age 4 years. His previous course was complicated by "lymphoma" (details not available) diagnosed in 1985 and treated with chemotherapy, CD4 lymphopenia, splenomegaly, thrombocytopenia, and recurrent infections (pneumonia, sinusitis, otitis, bronchitis), prompting 2 to 3 hospital admissions every year. He had been on intravenous immunoglobulins (IVIGs) for the preceding 12 years with trough IgG levels consistently above 800 mg/dL. He was first seen in our clinic in April 2004. At the time, he had an IgG level of 923 mg/dL (trough level) and nondetectable IgA, IgM, or IgE. His peripheral blood lymphocytes showed significant proliferation in response to concanavalin A, pokeweed mitogen, and alloantigen. In December 2002, the patient presented with fever (102°F) and axillary lymphadenopathy. The axillary lymphadenopathy progressed rapidly, reaching a diameter of 4 cm in a few weeks. Excisional lymphadenopathy biopsy showed necrotizing granulomatous lymphadenitis. There was no evidence of malignancy. No organisms were identified on acid-fast bacillus, fungal, and Gram stains; cultures were negative for bacteria, mycobacteria, and fungi. Itraconazole was started for presumed histoplasmosis.

Two months later, he was admitted with high-grade fever and worsening axillary and inguinal lymphadenopathy. Computed tomography (CT) scan showed massive mediastinal, paratracheal, and paraaortic lymphadenopathy (largest, 2.6 cm). Splenomegaly was stable at 19 cm.

Right axillary lymphadenopathy aspiration showed granulomatous inflammation with necrosis. Bone marrow biopsy was mildly hypercellular with no evidence of infection or malignancy. Flow cytometry showed no monoclonal lymphocyte populations. Stains and cultures from lymphadenopathy aspirate and bone marrow biopsy were negative for all microorganisms. He was treated with empiric oral antibiotics with no response.

In May 2003, he was readmitted with abdominal pain and daily high-grade fever spikes of 104°F. On CT scan, he had a 4.6-cm × 3.6-cm left psoas abscess and bilateral inguinal abscesses and adenopathy. Abscess aspirate and

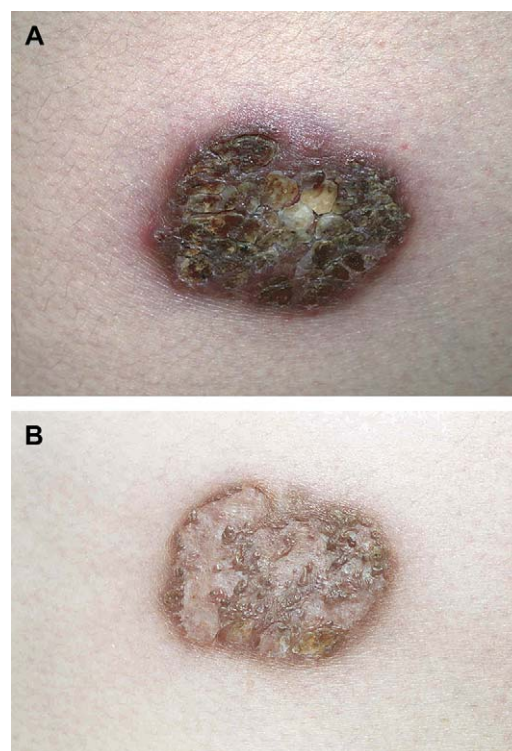


FIG 1. A, Skin plaque at baseline. B, Marked improvement 2 weeks after the third infusion.

groin and axillary excisional biopsies showed caseating granulomatous inflammation. Stains and cultures from all specimens were again negative. Because common infections were ruled out, an inflammatory etiology was entertained, and prednisone was started. The fever resolved, but the lymphadenopathy decreased only minimally in size.

In November 2003, he developed a rapidly expanding skin plaque over his back as prednisone was tapered (Fig 1, A). Biopsy showed noncaseating granulomas, and cultures were negative. The lesion continued to progress despite increasing prednisone and continuing IVIG treatment.

In May 2004, CT scan showed massive mesenteric and retroperitoneal lymphadenopathy (largest measuring 3.6 cm × 2 cm) and splenic abscesses (Fig 2, A). Spleen abscess aspirate showed marked necrosis with no clear granulomas. Liver biopsy was performed because of elevated liver function tests and showed focal sinusoidal congestion and no granulomas. Cultures from spleen and liver samples were again negative.

Because the patient's granulomatous inflammation continued to progress despite aggressive use of corticosteroids and IVIG, we thought that anti-TNF therapy may be helpful. Infliximab is effective in the treatment of Crohn's disease,⁵ a disorder characterized by granulomatous inflammation, and the use of infliximab has been associated with the reactivation of tuberculosis, thought to be a result of the breakdown of granulomas.⁵

Infliximab was started in June 2004. He received 5 mg/kg every 3 weeks for a total of 4 infusions. The skin plaque improved quickly and markedly (Fig 1, B). The splenic

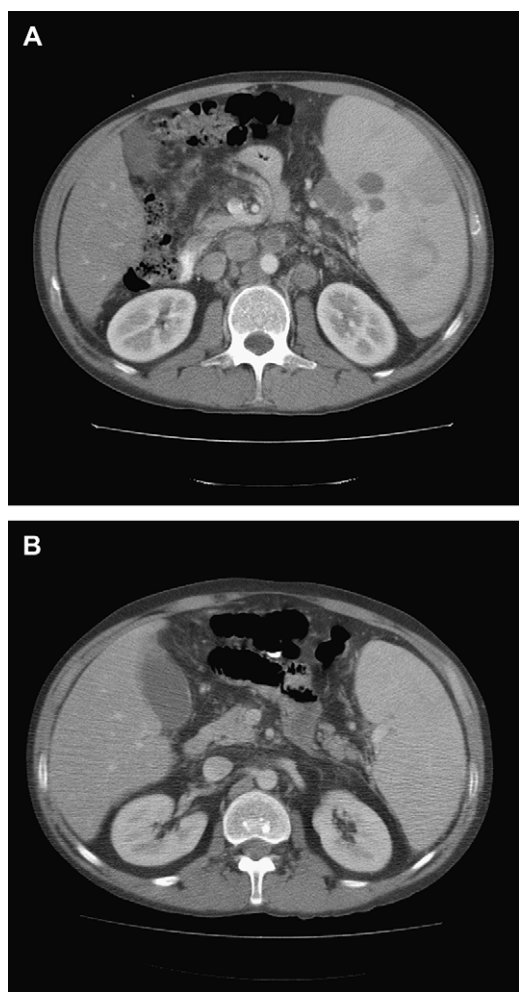


FIG 2. A, CT scan in May 2004 showing splenic abscesses and marked retroperitoneal lymphadenopathy. B, By October 2004, the splenic abscesses and retroperitoneal lymph nodes were almost completely resolved.

abscesses and the mesenteric and retroperitoneal lymphadenopathy were almost completely resolved (Fig 2, B). One year later, he continues to be free of granulomas.

Corticosteroids are usually used to treat noncaseating granulomas in CVID; however, they are not always effective. Other agents have been used with variable degrees of success, including IVIG, cyclosporine, IL-2, and etanercept. Caseating granulomas pose the additional challenge of thoroughly ruling out infectious causes. Two patients with CVID have been described, with caseating granulomas of the skin and viscera in one and only the skin in the other.^{3,4} Corticosteroids were beneficial in both patients. Our patient, however, did not respond to steroids, prompting the consideration of other modalities of treatment.

TNF- α appears to be necessary for the formation and maintenance of granulomas. Kindler et al⁶ showed that, in a mouse model of tuberculosis, injection of anti-TNF antibody interfered with the formation of granulomas in newly infected animals and caused the regression of granulomas in animals with established infection. Data

suggest that TNF- α increases the ability of macrophages to phagocytose and kill mycobacteria, stimulates apoptosis of infected macrophages, and regulates the expression of chemokines, chemokine receptors, and adhesion molecules involved in the formation of granulomas.⁷ Although most available information on the pathogenesis of granulomas is derived from the study of mycobacterial infections, the same mechanisms appear to be involved in the formation and maintenance of noninfectious granulomas as well.⁸

Among the anti-TNF agents available at that time (infliximab and etanercept), infliximab was thought to be more appropriate in our patient for multiple reasons: (1) it has a longer half-life (10.5 days vs only 3 days for etanercept); (2) it has proven efficacy in Crohn's disease, a granulomatous disorder, whereas etanercept does not; and (3) it is also associated with a higher rate of reactivation of latent tuberculosis infections than etanercept.⁹ It was thought that these characteristics are likely to reflect a superior antigranuloma effect, and this appears to be the case.

The marked success of infliximab in controlling the granulomatous inflammation in our patient indicates that it might prove to be invaluable in the treatment of CVID-associated granulomas, especially when standard therapies fail.

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