Infliximab (Anti–Tumor Necrosis Factor \( \alpha \) Antibody)

A Novel, Highly Effective Treatment of Recalcitrant Subcorneal Pustular Dermatosis (Sneddon-Wilkinson Disease)

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

**REPORT OF A CASE**

A 79-year old woman presented with a 7-year history of subcorneal pustular dermatosis (SPD). Primary lesions presented as widespread symmetrical eruptions with erythema and flaccid pustules of up to 5 mm in diameter (Figure 1A). Diagnosis was based on the clinical symptoms and the characteristic histologic finding of subcorneal sterile pustules in several skin biopsy specimens (Figure 2A). The results of indirect and direct immunofluorescence analyses were negative (not shown). The clinical course was resistant to multiple therapeutic trials including colchicine, retinoids, systemic glucocorticosteroids, UV phototherapy, azathioprine, and azulfidine. Dapsone treatment had to be discontinued because the patient developed hemolytic anemia. A year prior to presenting to our department, the patient was diagnosed with breast cancer and underwent ablative surgery with dissection of the regional axillary lymph nodes. At the time of admission to our department for treat-

![Figure 1. Upper chest region before (A) and after (B) intravenous treatment with infliximab (5 mg/kg).](image-url)
ment of an extensive flare-up of SPD, the patient had no signs of internal disorders or malignancy; there was no paraproteinemia. The patient had been taking no medication for 6 months when she presented with generalized erythema and widespread partly confluent pustules on the legs, thighs, forearms, trunk, and abdomen. The clinical course of SPD was finally recalcitrant despite a therapeutic trial with acitretin (0.6 mg/kg per day) and methylprednisone (1.3 mg/kg per day), which had been effective at an earlier disease stage.

THERAPEUTIC CHALLENGE

Dapsone,\textsuperscript{1,2} vitamin E,\textsuperscript{1} colchicine,\textsuperscript{1,2} etretinate,\textsuperscript{1,5} phototherapy (psoralen UV-A), narrowband UV-B phototherapy,\textsuperscript{5} methotrexate,\textsuperscript{7} and systemic glucocorticosteroids have been reported effective in treating SPD. Dapsone treatment is the first-line therapy but must be discontinued in some cases because hemoglobinemia or hemolytic anemia develops. The other therapeutic options are occasionally effective.\textsuperscript{1-7} In our patient, SPD was finally successfully controlled after several relapses by a maintenance therapy consisting of acitretin and methylprednisone. However, the disease was eventually unresponsive to this treatment. Skin lesions progressed, and the overall condition deteriorated accompanied by an increase of cellular and serological markers of inflammation (Figure 3).

SOLUTION

After admission for flaring SPD, the patient received a 10-day course of acitretin (0.6 mg/kg per day) and methylprednisone (1.3 mg/kg per day). Despite this therapy, the patient experienced progressive pustular eruptions accompanied by increased cellular and serological markers of inflammation (Figure 3). The reported association of SPD with pyoderma gangrenosum,\textsuperscript{8} rheumatoid arthritis,\textsuperscript{9,10} and inflammatory bowel diseases\textsuperscript{8,10} led to a therapeutic trial with infliximab (Remicade; Centocor BV, Leiden, the Netherlands), a chimeric anti–tumor necrosis factor α (TNF-α) antibody proven highly effective in the treatment of inflammatory bowel diseases and rheumatoid arthritis.\textsuperscript{11-14}

Prior to treatment with infliximab, workup to exclude evidence of occult infection included chest radiography, urinalysis, and abdominal ultrasound. Infliximab was given as a single intravenous dose of 5 mg/kg over 2 hours without any adverse effects. Within 24 hours after infusion of infliximab, the number of peripheral granulocytes and the concentration of C-reactive protein (CRP) rapidly declined to normal levels (Figure 3). The patient’s overall condition improved dramatically, and the pustules disappeared leading to scaling of the affected skin within 2 days (Figure 1B). Clinically and histologically, all the pustules vanished (Figures 1 and 2). The dose of oral methylprednisone was tapered to 0

Figure 2. Skin pathologic photomicrograph before (A) and after (B) treatment with infliximab.

Figure 3. Cellular (leukocytes) and serological C-reactive protein (CRP) markers of inflammation during therapy with infliximab. Elevated leukocyte counts and CRP concentrations immediately declined to normal levels after infliximab treatment (arrows indicate the days of intravenous infliximab administration).

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over 3 days. Acitretin treatment was continued at a dose of 0.4 mg/kg per day. Twelve days after infusion of infliximab, new pustules developed on the forearm accompanied by an increase of blood leukocytes. On day 14, infliximab was again administered intravenously at 5 mg/kg leading to complete remission within 1 day. Seventeen days after the second infliximab infusion, new erythematous papules, but no pustules, developed on the trunk and arms associated with an increase of peripheral inflammatory cells (Figure 3). This mild relapse was highly responsive to oral methylprednisone treatment given initially at 1.0 mg/kg per day. The skin condition improved within 24 hours and completely resolved over a 3-month period under treatment with methylprednisone (0.4 mg/kg per day) and acitretin (0.4 mg/kg per day). For the past 6 months, the patient has remained in complete remission on a maintenance therapy with acitretin (0.16 mg/kg per day).

Immunohistologic analysis of a skin biopsy specimen taken immediately before treatment with infliximab demonstrated an inflammatory infiltrate composed predominantly of CD15+ neutrophils, CD4+ and CD8+ T lymphocytes (not shown), and CD68+ cells (macrophages, monocytes, and lymphocytes; not shown). The CD15+ granulocytes accumulating in a pustule showed strong expression of TNF-α (Figure 4A). The inflammatory infiltrate had disappeared in a skin biopsy specimen taken 7 days after the first infliximab infusion, demonstrating a prolonged anti-inflammatory and TNF-α-suppressive effect (Figure 4, B). In summary, clinical remission of SPD was accomplished by an immediate reduction of inflammatory cells in the skin lesions and peripheral blood of the patient.

**COMMENT**

Subcorneal pustular dermatosis was first described in 1956 by Sneddon and Wilkinson as a chronic relapsing disorder histologically characterized by sterile, subcorneal pustules filled with neutrophils. This vesicopustular disorder mainly affects middle-aged women. The axillae, groin, abdominal, and flexural sites of the proximal parts of the limbs are most often involved, while the face and mucous membranes are usually spared. The etiology is unknown, but associations with paraproteinemia, pyoderma gangrenosum, rheumatoid arthritis, and inflammatory bowel diseases have been described. Even though SPD is a benign disorder, therapeutic management often remains challenging. A potential pathogenic role of TNF-α in SPD has been suggested by the finding that a patient with SPD had significantly elevated serum and blister fluid levels of TNF-α.

Tumor necrosis factor α belongs to the family of proinflammatory cytokines and plays a major role in host immune responses to infection, tumors, and foreign proteins. It is produced mainly by mononuclear phagocytes. Various biological effects of TNF-α have been described, including initiation of acute-phase responses, increase in body temperature, stimulation of migration of dendritic cells to lymph nodes, and activation as well as attraction of neutrophils. Tumor necrosis factor α has been identified as a critical mediator of inflammation in several inflammatory dermatoses including cutaneous vasculitides, lupus erythematosus, eczema, and psoriasis. Infliximab (Remicade) is a humanized-murine monoclonal anti-TNF-α antibody consisting of the variable domain (Fab) of mouse IgG attached to the constant region (Fc) of human IgG1. The antibody binds both the soluble subunit and the membrane-bound precursor of TNF-α and thereby neutralizes the biological activity of TNF-α. After its approval by the Food and Drug Administration in 1998, its therapeutic use has been extensively studied in rheumatoid arthritis and inflammatory bowel diseases such as Crohn disease. Furthermore, recent studies have shown promising results with the use of infliximab in the treatment of psoriatic
arthritis, psoriatic skin lesions, and pyoderma gangrenosum (unpublished data), conditions that are characterized by a neutrophilic inflammatory infiltrate. Since there is evidence that TNF-α may be involved in the pathogenesis of SPD, and because of the association of SPD with inflammatory bowel diseases, pyoderma gangrenosum, and rheumatoid arthritis, a therapeutic trial with infliximab was performed in our patient with severe recalcitrant SPD.

Over the years, the 79-year old patient had been treated with several medications. With each relapse, complete remission took at least 2 to 3 weeks to achieve. Eventually, SPD became resistant to systemic treatment with glucocorticosteroids and acitretin. In contrast, administration of infliximab on 2 occasions led to an immediate resolution of infliximab on 2 occasions led to an immediate regression of cutaneous inflammation in our patient with severe recalcitrant SPD. We therefore propose the use of infliximab for the immediate control of severe, recalcitrant SPD.

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Minor infections may be aggravated in patients receiving infliximab, since it blocks TNF-α, a major pro-inflammatory cytokine and mediator of the host defense to infections. Patients should be monitored and immediately treated for infections. Our patient developed several herpetiform blisters on the lower lip and oral mucosa that were found positive for herpes simplex virus type 1 under direct immunofluorescence. The lesions resolved after 5 days of acyclovir treatment.

Subcorneal pustular dermatosis is characterized by the migration of neutrophils into the skin, leading to the formation of sterile pustules. Tumor necrosis factor α may be a principal chemotactic factor responsible for neutrophil accumulation in the skin, as evidenced by elevated TNF-α concentrations in serum samples and pustular lesions of patients with SPD. In fact, infliximab immediately stopped ongoing cutaneous inflammation in our patient’s SPD. We therefore propose the use of infliximab for the immediate control of severe, recalcitrant forms of this disorder.

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REFERENCES