Septic Shock after Treatment of Pyoderma Gangrenosum with Infliximab

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Sir,

Pyoderma gangrenosum (PG) is a destructive inflammatory skin disease, which can occur at any age. Fifty percent of cases are linked with inflammatory bowel diseases or rheumatoid arthritis (RA) (1, 2). The aetiology of PG is unknown.

Standard therapy consists of systemic corticosteroids combined with other immunosuppressive drugs. Furthermore, a positive effect of intravenous treatment with immunoglobulins has been reported (2).

Tumour necrosis factor (TNF) is one of the main mediators of septic shock symptoms, but it is also indispensable in initiating and maintaining the protective immune response against bacterial or fungal pathogens (3, 4).

Infliximab is a chimeric IgG_1 antibody against TNF-α (5). The most important side-effects of anti-TNF therapy are probably the increased risk of severe infections without characteristic clinical signs of sepsis (6, 7) and the reactivation of mycobacterial infections (8). Infliximab is licensed for the treatment of chronic inflammatory bowel disease. Since PG is often associated with Crohn's disease, many patients with concurrence of both diseases receive infliximab treatment (9). Additionally, controlled studies have documented the efficacy of infliximab in PG (10). We report here on a patient with PG who developed septic shock during treatment with infliximab.

CASE REPORT

A 60-year-old male patient with reduced general condition was admitted to our clinic with a diagnosis of PG. Therapy with prednisolone alone or in combination with mycophenolatmofetil, cyclophosphamide or alprostadil infusions, local therapy with tacrolimus ointment (0.3%) and surgical interventions had been performed, but without achieving control. No associated inflammatory bowel diseases, paraproteinaemia, leukaemia or RA had been diagnosed.

At the time of presentation a widespread ulceration (19 × 12 cm) with livid-erythematous undermined borders and remnants of blistered epidermis on the distal left lower leg indicated PG. He had two ulcers (17 × 11 cm and 5 × 9 cm) on the right lower leg with necrotic base, sharp necrotic demarcation and undermined borders surrounded by a livid-erythematous coloured margin (Fig. 1). Blood tests showed a leukocytosis with 12210/µl, C-reactive-protein (CRP) 8.06 mg/dl, creatinine 1.5 mg/dl and a normochromic and normocytic anaemia. Physical examination showed no lymphadenopathy, and the liver and spleen were impalpable. A skin biopsy showed mixed lympho- and leukocytic vasculitis. Microbiological analysis revealed high numbers of *Pseudomonas aeruginosa* and *Staphylococcus aureus* on the ulcers.

Wound care was performed with silver-containing dressings combined with a rehydrating gel. Furthermore, immunosuppressive treatment with cyclosporin A (550 mg) and prednisolone (100 mg) once daily was initiated. After 5 days of therapy, his serum creatinine increased and consequently cyclosporin A medication was reduced to 125 mg twice per day. Due to progressive growth of PG immunoglobulins i.v., 2 g/kg bodyweight (BW) administered over 4 consecutive days every 4 weeks, were added. After significant improvement the patient developed new, painful blisters on the left thigh, followed by progressive tissue necrosis and enlargement of all ulcers shortly after the second cycle.

Due to the failure of all major treatments reported to be effective in PG, we stopped cyclosporin A and administered methotrexate (15 mg weekly) and concomitant therapy with prednisolone (75 mg per day). After excluding lung tuberculosis we started systemic therapy with the anti-TNF monoclonal antibody infliximab, 5 mg/kg BW, administered over 6 h. Immediately after treatment and the following day the patient felt tired but otherwise well. He had no fever, no diarrhoea, a blood pressure of 120/70 mmHg and no significant changes were detected in the laboratory parameters. After 24 h the patient seemed confused, but a psychiatric examination was inconspicuous. After 36 h he became increasingly confused, disoriented and agitated. After 48 h we observed an abrupt increase in pulse from 80 beats/min to 155 beats/min, concomitant diarrhoea, and increased creatinine (1.4 mg/dl to 1.8 mg/dl) and CRP levels (10 mg/dl to 27 mg/dl). The patient did not have hypotension. His body temperature was slightly elevated, to 37.2°C. He was transferred to the intensive care unit, where he was treated with linezolid, ciprofloxacin, tazobactam/piperacillin and fluconazole. He rapidly developed thrombocytopaenia and leukopaenia and his general condition deteriorated. Blood cultures proved sepsis with *S. aureus* and *P. aeruginosa*. After an intermediate improvement the ulcerations progressed again when the effect of anti-TNF therapy ceased. Finally, the right lower leg had to be amputated due to abscess formation. After surgery the PG progressed further. Immunosuppressive treatment with cyclophosphamide and prednisolone did not halt the PG and the patient eventually died of liver and kidney malfunction in septic shock after 2 months of intensive care.

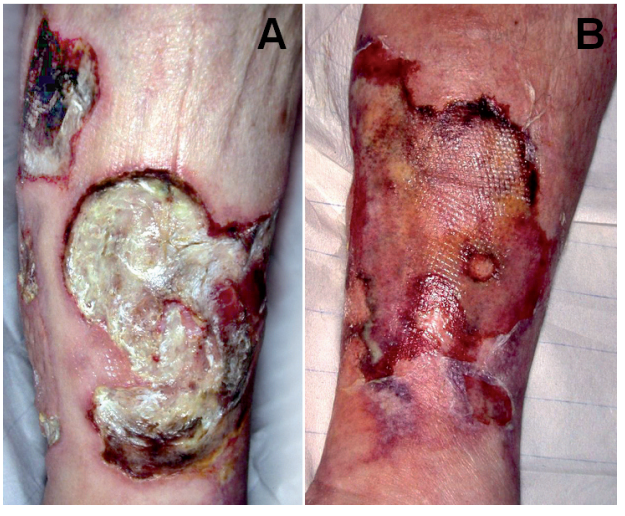

Fig. 1. Ulcers on (A) the right lower leg and (B) the left lower leg on admission.

DISCUSSION

In the early 1990s it was clearly demonstrated that anti-TNF treatment can control signs of septic shock in rodents and even humans (11, 12). However, since TNF also plays an important role in regulating the protective inflammatory response against pathogens, it has a double-edged function (3). TNF-α is necessary for the containment of intracellular infections, supposedly by inducing apoptosis in immune cells, e.g. infected macrophages (4). Clinical studies have shown that TNF-α inhibitors can promote the fatal course of septic shock rather than prevent it (6, 11).

TNF-α inhibitors, such as infliximab, can be an effective treatment even in cases of long-lasting PG with or without concomitant intestinal bowel diseases (9, 10, 13). Brooklyn et al. (10) reported a remission rate of up to 21%. Serious infections occur in about 18% of patients treated with infliximab or etanercept (7). Clinical trials with placebo control do not suggest that anti-TNF therapy increases the frequency of infections (10); however, it may seriously aggravate the course of bacterial infections (7).

In a randomized trial of infliximab in PG, 1 of 29 patients developed multi-organ failure following *S. aureus* septicaemia and died 7 days after the administration of infliximab (10). We hypothesize that, due to the obligatory concomitant infection of the ulcers, patients with chronic skin ulcers, e.g. PG, have an increased risk of serious infections while undergoing TNF-α inhibitor therapy.

A second important aspect is the atypical clinical course of the systemic inflammatory response syndrome. Kroesen et al. (7) reported that the course of systemic infections is often fulminant, with only slight alterations in well-being and, except for an increasing CRP level, hardly any preceding laboratory signs. Pro-inflammatory cytokine TNF-α induces acute phase responses and the well-known clinical and laboratory signs of infection, such as malaise and fever, thus anti-TNF-α drugs severely alter the acute phase response, so that sepsis starts insidiously with dramatic or acute presentations (6).

Due to its long half-life of 8–9.5 days, the pharmacological effects of infliximab are difficult to control once patients develop sepsis. It is therefore critical for the clinician to be aware of the risks of TNF-α inhibitors, such as masked infections or atypical fulminant course of endotoxic shock. Goode et al. (6) proposed treating patients "as if they were significantly immunocompromised".

Since severe infections are often recognized only at an advanced stage and can be poorly controlled by high-dose intravenous antibiotics, there is a strong need for early and effective therapy. Some authors have suggested the use of prophylactic treatment with antibiotics, e.g. in patients with fistulating Crohn's disease (14). Patients with additional immunosuppressive therapies, diabetes, other immunosuppressive diseases, wounds, surgery or artificial joints are at particular risk of sepsis during anti-TNF-α therapy. To be able to control these risks, it is necessary to establish an individualized prophylaxis before starting anti-TNF-α treatment. Antibiotics that are specifically adapted to the individual wound flora may be considered necessary as prophylaxis.

REFERENCES

1. Ahmadi S, Powell FC. Pyoderma gangrenosum: uncommon presentations. Clin Dermatol 2005; 23: 612–620.
2. Reichrath J, Bens G, Bonowitz A, Tilgen W. Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. J Am Acad Dermatol 2005; 53: 273–283.
3. Echtenacher B, Mannel DN, Hultner L. Critical protective role of mast cells in a model of acute septic peritonitis. Nature 1996; 381: 75–77.
4. Keane J, Remold HG, Kornfeld H. Virulent Mycobacterium tuberculosis strains evade apoptosis of infected alveolar macrophages. J Immunol 2000; 164: 2016–2020.
5. Knight DM, Trinh H, Le J, Siegel S, Shealy D, McDonough M, et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol 1993; 30: 1443–1453.
6. Goode S, Tierney G, Deighton C. Life threatening intra-abdominal sepsis in patients on anti-TNF-alpha therapy. Gut 2006; 55: 590–591.
7. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford) 2003; 42: 617–621.
8. Ehlers S. Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept? Clin Infect Dis 2005; 41: 199–203.
9. Tan MH, Gordon M, Lebwohl O, George J, Lebwohl MG. Improvement of pyoderma gangrenosum and psoriasis associated with Crohn's disease with anti-tumor necrosis factor alpha monoclonal antibody. Arch Dermatol 2001; 137: 930–933.
10. Brooklyn TN, Dunnill MG, Shetty A, Bowden JJ, Williams JD, Griffiths CE, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. Gut 2006; 55: 505–509.
11. Fisher CJ, Agosti JM, Opal SM, Lowry SF, Balk RA, Sadoff JC, et al. Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The soluble TNF Receptor Sepsis Study Group. N Engl J Med 1996; 334: 1697–1702.
12. Abraham E, Wunderink R, Silverman H, Perl TM, Nasraway S, Levy H, et al. Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome. A randomized, controlled, double-blind, multicenter clinical trial. TNF-alpha MAb Sepsis Study Group. JAMA 1995; 273: 934–941.
13. Kaur MR, Lewis HM. Severe recalcitrant pyoderma gangrenosum treated with infliximab. Br J Dermatol 2005; 153: 689–691.
14. Herrlinger KR, Borutta A, Meinhardt G, Stange EF, Fellermann K. Fatal staphylococcal sepsis in Crohn's disease after infliximab. Inflamm Bowel Dis 2004; 10: 655–656.