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SHORT COMMUNICATION

Development of Necrotising Fasciitis in a Patient Treated for Rheumatoid Arthritis with Tocilizumab

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Necrotising fasciitis (NF) is a potentially lethal infection affecting subcutaneous tissue and superficial fascia that may progress to multiple organ failure, and the prognosis is often worse when the host is immunocompromised. The prognosis is influenced by early diagnosis and early surgical debridement (1). Biologic therapies have been used in treating intractable inflammatory diseases, including collagen disorders. When using such a treatment strategy, it is critical to be aware that the treated subject may be highly susceptible to infection. Tocilizumab is a humanised monoclonal antibody directed against the interleukin-6 (IL-6) receptor and is recognised as an excellent biologic treatment in inflammatory rheumatic conditions (2). However, we wish to highlight the fact that its use may be associated with serious adverse reactions such as NF. It is known that tocilizumab may completely suppress induced C-reactive protein (CRP) via neutralisation of IL-6 effects (3). In fact, there have been a few reports of infections and other adverse events in subjects treated with tocilizumab (4).

CASE REPORT

A 53-year-old Japanese man, who had been treated for 4 years with tocilizumab (8 mg/kg every 4 weeks) for rheumatoid arthritis (RA), developed leg ulcers 2 years after starting treatment. A skin biopsy was performed at the time and this showed leukocytoclastic vasculitis that was an extra-articular manifestation of RA. Two years later, he presented with redness around the left leg ulcer associated with inappropriate local treatment for the past 5 days. In addition, extensive haemorrhagic bulla formation and erosions were found around the left leg ulcer. He was admitted to a local hospital and treated with antibiotics for 2 days. Despite this, the redness spread from the left leg ulcer to the mid-calf, and he had difficulty walking due to severe pain.

He was referred to our hospital 24 days after the last tocilizumab administration. He presented with widespread purpura and sclerotic change with normal local temperature, extending from his left toe to mid-

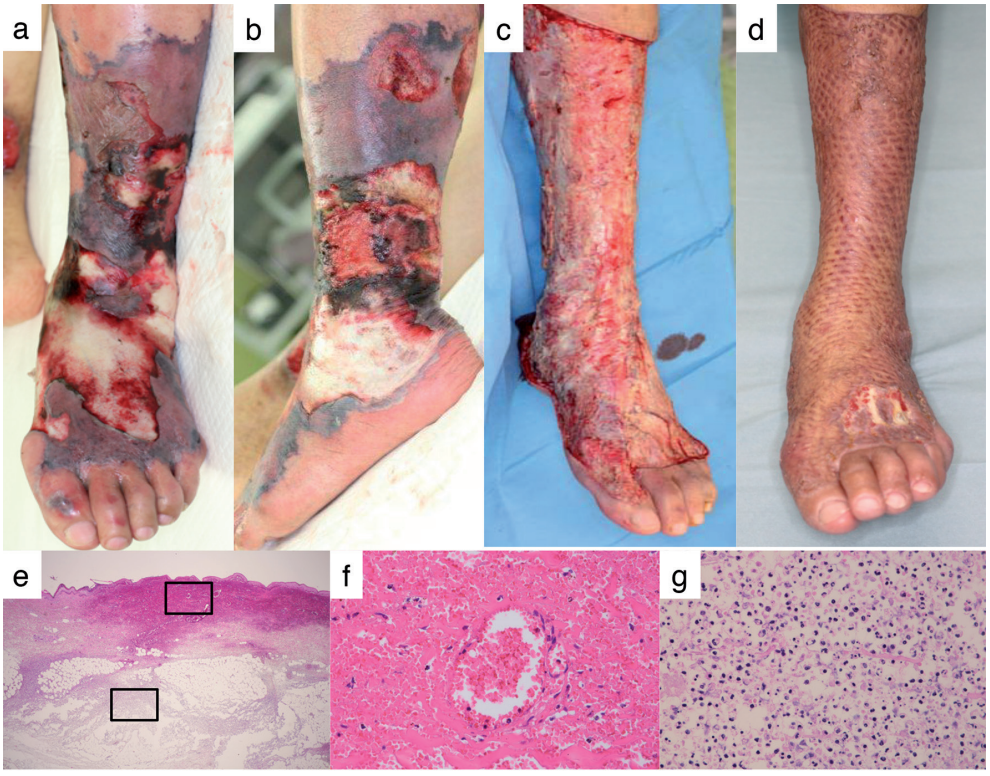

Fig. 1. Haemorrhagic bulla formation and sclerotic change extending from left toe to mid-calf are observed (a). Skin ulcer was observed near the foot joint for 2 years (b). Radical surgical debridement was performed 5 h after admission (c). A split skin graft was applied (d). Histopathological findings from haematoxylin- and eosin-stained tissue sections show presence of thrombi and severe neutrophil infiltration (e–g) (e: × 20; f and g: × 400).

calf (Fig. 1a, b). His vital signs were as follows: blood pressure, 161/92 mmHg; pulse, 108 beats/min; and body temperature, 36.9°C. Results of laboratory tests were as follows: white blood cell count, 22.1×10^9/l (neutrophils, 89%); haemoglobin, 9.8 g/dl; CRP, 25.3 mg/dl; sodium, 130 mEq/l; creatinine, 0.66 mg/dl; glucose, 154 mg/dl; serum IL-6, 218 pg/ml; and serum vascular endothelial growth factor (VEGF), 572 pg/ml. Computed tomography imaging of the affected regions on the lower left leg showed swelling and contrast enhancement in the subcutaneous tissue. Furthermore, exploratory incision of diseased skin exuded a watery, slightly scented fluid. Microbial culture tests revealed Group A Streptococcus heavy growth. Radical surgical debridement was performed 5 h after admission (Fig. 1c). On the second day of hospitalization, serum IL-6 and VEGF levels had decreased to 57.6 pg/ml and 255 pg/ml, respectively. The patient was treated in the intensive care unit post-surgery with intravenous penicillin G (24×10^6 U/day) and meropenem (3 g/day) and he gradually showed improvement. At day 21 after the initial debridement, a split skin graft was successfully transplanted (Fig. 1d), and he was discharged at day 70.

DISCUSSION

Histopathological findings from necrotic tissue revealed severe neutrophil infiltration, and occlusion of the vascular lumen by thrombi was detected (Fig. 1e-g). This type of occlusion in patients with NF has been previously described (5). In this case, serum VEGF levels dramatically decreased after debridement of necrotic tissue. It is known that VEGF contributes to growth of vessels in inflammatory diseases (6). Thus, we speculate that there is an association between occlusion of the vascular lumen in necrotic tissue and elevated serum VEGF levels in patients with NF.

Lack of constitutional symptoms in the presence of serious infection has been reported in RA patients treated with tocilizumab (7). Mild adverse events may often be overlooked and these may lead to lethal complications. We have identified 2 other published reports that have evaluated NF in patients who were treated with tocilizumab for RA (8, 9). In those cases, it was difficult to make an initial diagnosis of NF because the patients lacked typical laboratory findings, such as elevated CRP and white blood cell count. In the NF case described here, the CRP levels were abnormally high. It is possible that these controversial findings were influenced by the period of time since the final tocilizumab administration. However, all cases reported severe pain, and none of them described local warmth. Appropriate diagnostic methods, including computed tomography imaging, needle aspiration, and exploratory incision, have led to accurate diagnosis, and they can improve the prognosis of patients who develop NF following tocilizumab treatment.

Our experience highlights the fact that increased attention and low investigation threshold should be maintained in patients treated with tocilizumab. Early recognition and treatment of serious infections may improve prognosis in patients treated with biologics.

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