Lupus erythematosus (LE) profundus is a severe cutaneous lupus manifestation, which is commonly associated with ulceration and scar formation (1).

While systemic lupus erythematosus (SLE) is a multifactorial disease, SLE organ inflammation involves proinflammatory cytokines (2) and tumor necrosis factor (TNF)-α (3), in particular, which was found to be upregulated in several types of inflammatory lesions in SLE (4). Indeed, in observational studies and case reports, anti-TNF-α therapies have been reported to be beneficial in patients with SLE, and lupus nephritis, in particular (5). Less is known about the effect of TNF-α antagonists on manifestations of cutaneous LE (6, 7).

We describe here the case of a SLE patient with widespread LE profundus responding to induction therapy with infliximab and concomitant treatment with methotrexate (MTX).

CASE REPORT
A 36-year-old woman had a 15-year history of SLE. Cutaneous lesions initially presented as malar rash and erythematous plaques with fine scales in the face. She also developed mild arthritis and myositis and had been positive for anti-dsDNA antibodies and anti-nuclear antibodies (ANA). During the last year on hydroxychloroquine, she developed extended periorbital oedema, followed by severe ulcerations on the scalp and the back, leading to hair loss, pain, and depression (Fig. 1a). On the face, elevated red to violaceous plaques and smooth white atrophic scars with a tendency to spare the nasolabial folds were apparent. Large, deep ulcerations dominated on her scalp and back, reaching from the shoulders to the lower back. One inducing factor might have been an influenza vaccination that the patient received prior to the development of periordial oedema.

Apart from the cutaneous lesions, the physical examination was unremarkable. Plain X-ray films of her hands did not reveal erosions. Abdominal sonography only found cholecystolithiasis. Echocardiography excluded pericarditis. X-ray of the chest and magnetic resonance imaging (MRI) of the head found no evidence for pulmonary or central nervous system (CNS) involvement. No focal neurological symptoms were notable.

Laboratory examination showed anaemia of chronic disease (erythrocytes 3.92 cells/µl (normal 4.2–5.4), haemoglobin 6.4 mmol/l (7.4–10.7), haematocrit 0.33 (0.37–0.47)), lymphocytopenia (0.53 giga-particles/l (1.5–4)), elevated erythrocyte sedimentation rate (32/60: 32 one hour and 60 after two hours) and reduced serum complement components (C4 0.06 g/l (0.1–0.4), C3 0.55 g/l (0.9–1.8)). Elevated serum values were detected for serum amyloid A (9.7 mg/l (0.8–6.4)), lactate dehydrogenase (4.03 µmol/(s*l) (2.25–3.55)), gamma-glutamyl-transferase (3.22 µmol/(s*l) (< 0.7)) and immunoglobulin G (IgG) (16.6 g/l (7–16)). Other than that, differential blood count, thyroid, kidney and liver function tests, protein electrophoresis, C-reactive protein (CRP), myoglobin, aldolase, glucose, ferritin, as well as coagulation tests (Quick, Partial Thromboplastin Time, International Normalized Ratio) were unremarkable. A 24 h urine status did not show increased protein or albumin levels. Cryoglobulins and cryofibrinogen were absent.

Indirect immunofluorescence on Hep-2 cells showed an ANA titre of 1:640 with homogenous and fine granular staining of nucleoplasm and cytoplasm. Auto-antibodies against dsDNA detected by enzyme-linked immunosorbent assay (ELISA) were borderline (27 IU/ml) before therapy. Determination of IgG antibodies against dsDNA by Crithidia luciliae fluorescence test (CLIFT) did not detect positive antibodies at that time. Auto-antibodies against Ro, La, nucleosomes, histones, Ku, Mi-2, Jo-1, Sm and PmScl were undetectable. Tests for phospholipid-binding antibodies, beta2-glycoprotein I and circulating immune complexes were negative. Serum levels of interleukin (IL)-6 were normal, while TNF-α was slightly elevated (13.1 pg/ml (< 8.1)).

There was no clinical/serological evidence for systemic viral or bacterial infections, and specifically hepatitis A, B, and C serology was negative and a T-cell test for tuberculosis (T spot TB) was negative.
Histological examination of lesional skin from the shoulder showed perivascular lymphocytic cell infiltrate in the dermis and upper adipose tissue (Fig. 2a). Calcification was seen focally. In the subcutaneous adipose tissue, hyaline necrosis of adipocytes and signs of cytophagic, mainly lobular, panniculitis were present. Alcian blue staining revealed marked deposition of mucin within the dermis and adipose tissue. There were no signs of malignancy. Direct immunofluorescence staining demonstrated deposition of C3, IgM and weak IgG staining at the basement membrane zone. IgM was also found perivascularly. These findings were consistent with the diagnosis of lupus erythematosus profundus. Immunohistochemical staining revealed strong deposition of TNF-α in the whole epidermis, dermis and adipose tissue (Fig. 2b).

Immunofluorescence staining of non-lesional, not ultraviolet (UV)-exposed skin showed deposition of IgG, IgM and C3 at the basement membrane zone, in line with the diagnosis of SLE.

Prior treatment with hydroxychloroquine, azathioprine, MTX and intravenous immunoglobulin were not able to sufficiently control disease. Cyclophosphamide, rituximab and mycophenolate mofetil had to be discontinued because of severe, and, in part, life-threatening, adverse effects. We therefore decided to start therapy with the TNF-α blocker infliximab. The patient received 5 mg infliximab/kg body weight at weeks 0, 2, 6, 10 and 14, and concomitant treatment with 10 mg MTX once per week. Days after the first infusion ulcerations on the scalp responded vigorously, with granulation and epithelization. After 6 months of therapy no ulcerations were detectable on the scalp (Fig. 1b). The ulcerations on the back were deeper and did not respond so fast. Nearly complete epithelization required one further year.

After an induction regimen of five infusions of infliximab, the patient continued 20 mg MTX once per week and 200 mg hydroxychloroquine daily. Her skin disease remained in stable clinical remission for more than one year. Anaemia also improved (HG 7 mmol/l), but was still present, as were lymphocytopaenia and low complement (C4 0.06 g/l, C3 0.53 g/l). Infliximab did not induce clinical side-effects. However, during TNF blockade, anti-dsDNA antibodies increased to strongly positive concentrations (142 IU/ml) in ELISA and became positive (1:80) in the CLIFT. The increase was already detectable after the first 2 months of treatment. The level of anti-dsDNA antibodies remained stable thereafter and was not associated with renal involvement or other new organ manifestations.

DISCUSSION

This patient with severe LE profundus, responded rapidly to TNF-α blockade. Importantly, the induced remission remained stable during the next 12 months on MTX and hydroxychloroquine, which had not previously been sufficient to control disease.

The slower response of the ulcerations on the back might be related to the deeper primary ulcerations compared with the scalp and mechanical stress. In addition, permissive factors could contribute to the prolonged course in this patient, who was not able to stop smoking completely, which was identified as a provoking factor for LE in epidemiological studies (8).

The patient developed large periorbital oedema, described as a rare initial symptom in LE profundus (9). The subcutaneous tissue in the periorbital region is predisposed to oedema formation because the fluid cannot flow easily through the facia of the orbital rim (10). Histological examination of the affected orbital region has demonstrated a perivascular lymphohistocytic infiltrate possibly indicates immune complex vasculitis (11).

It is worthy of note that TNF-α blockade induced an increase in anti-dsDNA-antibodies in the patient which has also been seen in patients with SLE and rheumatoid arthritis (5, 12). SLE flares were not reported under TNF-α blockers, but drug-induced lupus do occur (13, 14). Therefore, and because of life-threatening adverse events in SLE patients on long-term TNF-α blockade (15), TNF-α-blockers probably should be used as an induction therapy only in patients with severe cutaneous LE.

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REFERENCES