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Successful Treatment of Recalcitrant Palmoplantar Pustular Psoriasis with Sequential Use of Infliximab and Adalimumab

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Key Words

Pustular psoriasis, treatment • Biologicals • Infliximab • Adalimumab • Tumor necrosis factor α

Palmoplantar pustular psoriasis (PPP) is characterized by recurrent crops of sterile intraepidermal pustules, erythema, fissuring and scaling confined to the palms and soles [1]. PPP may represent a variant of psoriasis, and some patients also have further psoriatic skin lesions on their bodies [2]. The majority of patients affected are women and smokers [1]. The disease causes considerable physical disability, and treatment regimes often remain unsatisfactory [3]. Previous case reports indicate that tumor necrosis factor (TNF) inhibitors may be helpful in the treatment of pustular psoriasis [4–10]. However, some reports have also described paradoxical induction of pustular psoriasis by TNF inhibitors and have cautioned the use of these agents in PPP [11–13].

Case Report

A 48-year-old female was referred to our department with a history of recurrent pustules appearing predominantly on her feet for 1 year. The patient also suffered from psoriatic arthritis, depression, asthma and was a heavy smoker (approx. 30 pack-years). Her skin and joint involvement caused disabling pain. Bacteriological and mycological tests of the skin lesions were negative. Histological examination was consistent with PPP. The patient failed to respond to several treatments including topical preparations (potent steroids, vitamin D analogs, tazarotene, tar, tacrolimus), phototherapy (PUVA), acitretin (40 mg daily) and methotrexate (15 mg weekly). Due to the recalcitrant course, the patient was hospitalized for further therapeutic intervention. After obtaining her informed consent, induction treatment (at weeks 0, 2 and 6) with the chimeric anti-TNF antibody infliximab was initiated. The clinical appearance of her feet before initiation of monotherapy with infliximab (5 mg/kg) is shown in figure 1a and b. A marked improvement of her skin lesions (fig. 1c and d) and joint symptoms was already notable within 2 weeks after the 1st infusion of infliximab, and further amelioration was seen after the

2nd and 3rd infusions (fig. 1e and f). However, treatment with infliximab was discontinued due to an infusion-related reaction with polyarthralgia, myalgia and fever after the 3rd infusion. Although acitretin (30 mg daily) was reintroduced, some painful pustular skin lesions, erythema, fissuring and scaling started re-appearing on her feet approximately 8 weeks after the 3rd infusion with infliximab. After obtaining her informed consent, treatment with the fully human anti-TNF antibody adalimumab (40 mg subcutaneous injection biweekly) was initiated. Due to partial response after 4 weeks, the dosage was increased to weekly subcutaneous injection of 40 mg adalimumab, which subsequently led to further amelioration (fig. 1g and h). Therapy with adalimumab (40 mg weekly) was well tolerated except for a weight gain of 5 kg within the last 3 months, which the patient attributed to therapy.

In order to investigate cellular alterations and expression of TNF- α during initial treatment with infliximab, punch biopsy specimens (5 mm) were obtained from lesional skin before beginning therapy and from skin adjacent to the first biopsy at week 2 (1 day after the 2nd infusion). Biopsy specimens were routinely processed for histology (HE staining) as well as for immunohistochemistry using the ABC-AP method as described previously [14]. The following primary antibodies were used: CD3 (clone: PS1, Novocastra, Newcastle-upon-Tyne, UK), CD4 (clone: 1F6, Novocastra), CD8 (clone: C8/144B, Dako Cytomation, Glostrup, Denmark), neutrophil elastase (clone: NP57, Dako Cytomation), CD1a (clone: O10, Dako Cytomation), CD68 (clone: PG-M1, Dako Cytomation) and HLA-DR (clone: CR3/43, Dako Cytomation). Immunofluorescence staining was performed with anti-TNF antibodies (clone: 28401, R&D Systems, Minneapolis, Minn., USA) as described previously [15].

Representative HE and immunohistochemical staining samples before therapy and at week 2 are shown in figure 2a–p. In correlation with the patient's clinical improvement, a significant decrease in different leukocyte populations including T cells (CD4+ T helper cells and CD8+ T cytotoxic cells), neutrophils, CD1a dendritic cells and CD68 macrophages was found at week 2 (fig. 2). Initially, skin lesions also showed a marked expression of the activation marker HLA-DR+ particularly in the dermal infiltrate, which also decreased but still remained evident at week 2. Furthermore, strong immunofluorescence for TNF- α was observed particularly in the cellular infiltrate of the skin lesion obtained before therapy (fig. 3a). In correlation with the reduction of the proinflammatory infiltrate, a significant decrease in TNF- α immunofluorescence was observed at week 2 (fig. 3b).

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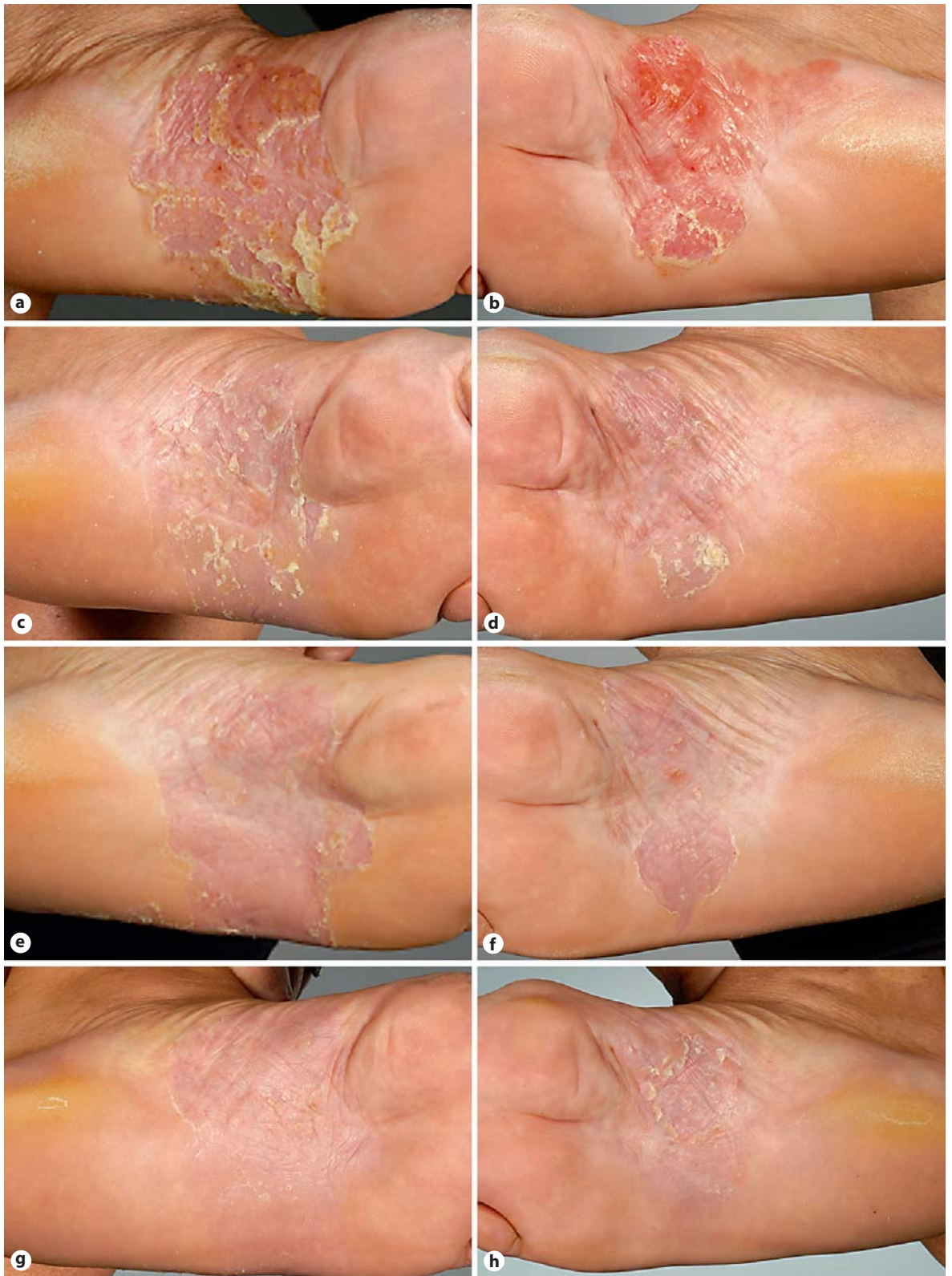


Fig. 1. **a, b** Pustular psoriasis of the soles before induction treatment with infliximab. **c, d** At week 2 (1 day after the 2nd infusion). **e, f** At week 6 (during 3rd infusion). Thereafter, treatment with

infliximab was stopped, and therapy with adalimumab was started 8 weeks later. **g, h** After 12 weeks of treatment with adalimumab.

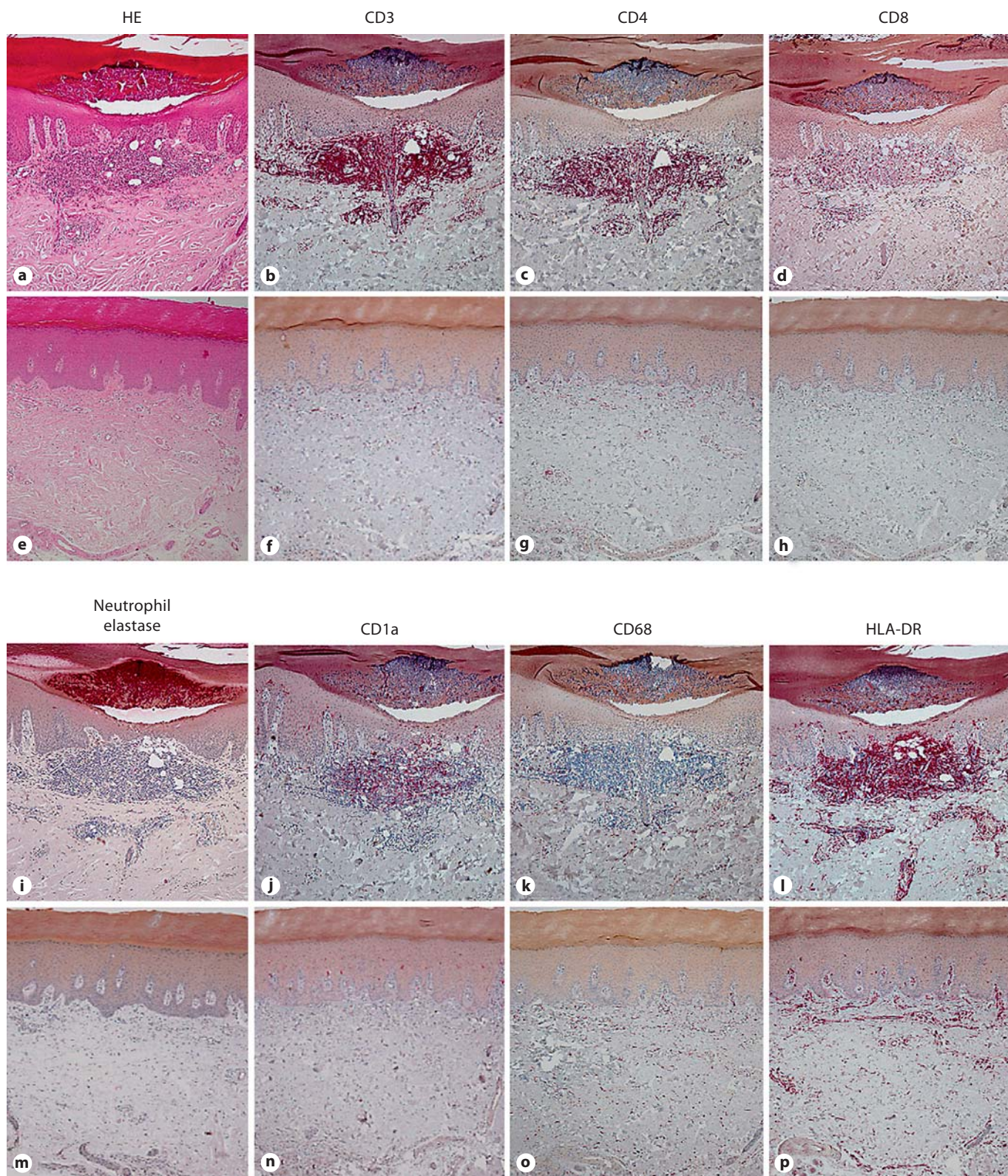


Fig. 2. Histological (HE staining) and immunohistochemical findings of different leukocyte populations showing a significant reduction of the proinflammatory infiltrate. **a-d, i-l** Before treat-

ment with infliximab. **e-h, m-p** At week 2 (1 day after the 2nd infusion). Original magnification $\times 100$.

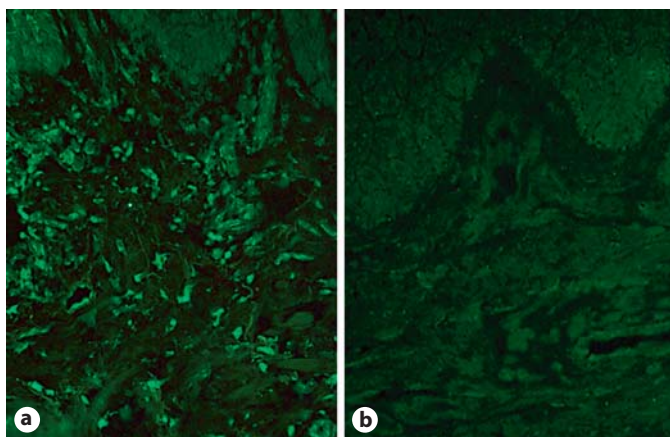


Fig. 3. **a** Immunofluorescence staining for TNF- α before induction treatment with infliximab. **b** Marked reduction of TNF- α immunofluorescence at week 2 (1 day after the 2nd infusion). Original magnification $\times 200$.

Discussion

The therapy of PPP is challenging since it very often resists conventional topical treatments. Usually phototherapy or systemic treatment options like retinoids, methotrexate or cyclosporine A are used but they often reveal various side effects with an unsatisfactory therapeutic gain. Based on the pivotal pathophysiological role of TNF- α in psoriasis and the successful treatment of chronic plaque psoriasis with TNF antagonists, clinicians have begun using these agents in the treatment of other inflammatory skin diseases including distinct phenotypes of psoriasis. Some previous case reports have shown that anti-TNF treatment may be effective in localized and generalized forms of pustular psoriasis [4–10]. Similarly, our case demonstrates that induction therapy with infliximab can lead to a rapid resolution of severe recalcitrant PPP. Furthermore, it shows that in case of nontolerability to the chimeric anti-TNF antibody infliximab this agent can be replaced by the fully humanized anti-TNF antibody adalimumab. Although both anti-TNF antibodies were effective, induction therapy with infliximab at a dose of 5 mg/kg revealed a more rapid resolution. A satisfactory clinical response with adalimumab was less apparent and was only achieved with weekly injections at a dose of 40 mg. Interestingly, a previous report also indicates that switching from infliximab to another TNF antagonist like etanercept may be useful in the treatment of psoriasis [16].

In correlation with the rapid clinical improvement during therapy with infliximab, a strong reduction of various leukocyte populations including T cells (CD3, CD4 and CD8), neutrophils (neutrophil elastase), macrophages/monocytes (CD68) and dendritic cells (CD1a) was notable. Recent research into the pathogenesis of psoriasis indicates that besides activated T cells, components of the innate immunity like macrophages and dendritic cells are crucial in the development of psoriasis. These cells are the main producers of type 1 cytokines like γ -interferon and TNF- α , which dominate the cytokine profile in psoriasis. TNF- α has been shown to induce the expression of various cell adhesion

molecules like intercellular adhesion molecule 1 and chemokines like interleukin 8, growth-regulated oncogene α , monocyte chemoattractant protein 1 which are particularly abundant in pustular psoriasis and involved in the recruitment and activation of neutrophils and other leukocytes. Thus, neutralization of local TNF production by anti-TNF antibodies appears to interfere at a central pathogenic step in the development of pustular psoriasis, presumably by blocking trafficking of leukocytes into the skin and induction of apoptosis in a part of these cells.

Although our patient showed a clear benefit from treatment with infliximab and adalimumab, it should be kept in mind that anti-TNF therapy may not always be helpful in patients with pustular psoriasis [11]. In fact, recent reports indicate that these agents may even induce or exacerbate pustular psoriatic lesions in some patients [12, 13, 17]. The underlying mechanisms leading to the paradoxical induction of pustular psoriasis are unknown, and future studies are warranted to elucidate which patients may preferably respond to anti-TNF treatment in pustular psoriasis.

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