

Cutaneous Drug Eruption with an Interface Dermatitis Pattern due to Anti-tumour Necrosis Factor-alpha Agents: A Relevant Class-effect

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Cutaneous adverse events have been described previously in patients receiving treatment with tumour necrosis factor (TNF)- α blocking agents (1). There are increasing reports of inflammatory cutaneous disorders, such as eczema, psoriasis and lichenoid eruption, induced, paradoxically, by TNF- α blockade. We report here two cases of atypical lichenoid drug eruptions with interface dermatitis histology that occurred during therapy for psoriasis and psoriatic arthritis with the TNF- α blocking agents infliximab and etanercept.

CASE REPORTS

Case 1

A 71-year-old man who had had psoriatic arthritis (with limited cutaneous involvement) for 26 years that had proved resistant to conventional treatments such as methotrexate (MTX) and non-steroidal anti-inflammatory drugs (NSAIDs) was initiated on infliximab (5 mg/kg) monotherapy. At the same time, arterial hypertension and osteoporosis were treated with olmesartan, alfosozine and vitamin D3. There was no family history of psoriasis or any other skin disease. After a complete, initial remission of cutaneous and articular psoriatic manifestations the patient developed an acute symmetrical diffuse eruption in the sixth week. Atypical papular, erythematous-squamous lesions involved the scalp, the trunk and the extensor area of the arms and legs with intense itching not previously reported by the patient (Fig. 1a). Histological examination of the lesional skin revealed an interface dermatitis pattern with vacuolization of basal keratinocytes and a band-like lymphocytic infiltrate in the superficial dermis (Fig. 1b). Direct immunofluorescence of the perilesional skin was negative, as were laboratory investigations for autoimmunity (anti-nuclear and anti-ds DNA autoantibodies). Infliximab therapy was discontinued and cyclosporin A (CsA), 3 mg/body weight/daily, was initiated. After one week of

CsA therapy and an improvement in desquamation the cutaneous lesions revealed marked papular features and a dark-red violaceous hue. After 12 weeks of CsA therapy clinical remission, with secondary hyperpigmentation, was obtained. A follow-up visit after 3 months documented a slight improvement in the hyperpigmentation, but with an initial recurrence of joint pain, which required retreatment with CsA.

Case 2

A 53-year-old man with severe psoriatic arthritis with extensive skin involvement had undergone combination therapy with MTX on a continuous basis, and etanercept on an intermittent basis, since 4 years. Previous systemic treatments (phototherapy, CsA and retinoids) had proved ineffective or were contraindicated due to complex comorbidity (ischaemic heart disease, arterial hypertension, dyslipidaemia and type II diabetes) and coexisting therapies (zofenopril, acetylsalicylic acid, repaglinide, metformin, escitalopram and alprazolam). In May 2008 a fourth cycle of etanercept (50 mg/week), with ongoing MTX (10 mg/week), was started due to a psoriasis flare. After 12 weeks, clearing of skin lesions and complete remission of articular symptoms was achieved. In the 16th week the patient presented erythematoviolaceous papular lesions asymmetrically localized on the temporal region, the wrists and the back of the right hand (Fig. 2a) with intense itching. Histopathological findings were of typical interface dermatitis pattern (Fig. 2b). Direct immunofluorescence and autoantibodies assay results were negative. Both etanercept and MTX were stopped as a precaution, introducing only topical therapy (clobetasole-propionate ointment). After 4 weeks there was a remission of papular lesions with secondary hyperpigmentation. At 8 weeks of follow-up the patient presented widespread erythematous-squamous lesions and acute inflammatory joint-pain, as seen in typical psoriasis. A first-time course of adalimumab (40 mg/every other week) was then initiated, leading to complete remission of cutaneous lesions and joint-pain after 12 weeks. Adalimumab monotherapy was well tolerated and was continued for 24 weeks without any relapse of psoriatic or other cutaneous lesions.

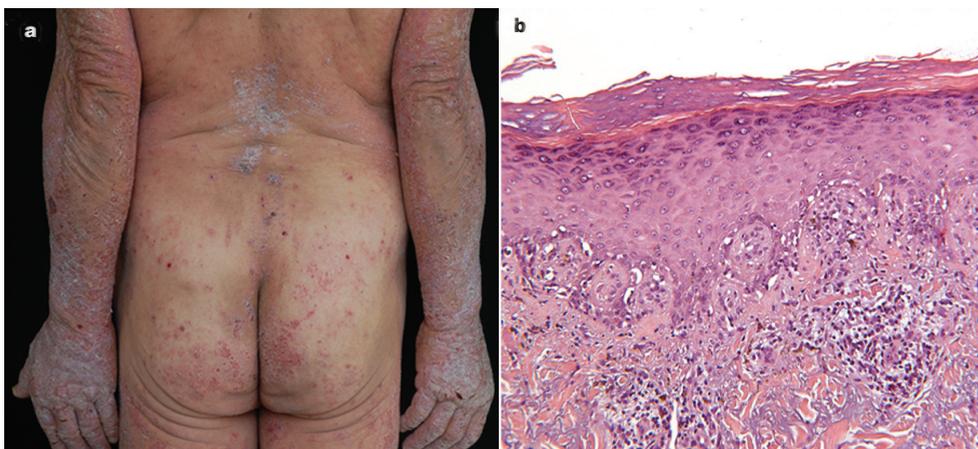


Fig. 1. Case 1. (a) Symmetrical diffuse papular, erythematous-squamous lesions on the trunk and extensor area of the arms. (b) Interface dermatitis pattern with vacuolization of basal keratinocytes, hypergranulosis, band-like lymphocytic infiltrate in the superficial dermis and squamatization of the epidermis ($\times 100$).

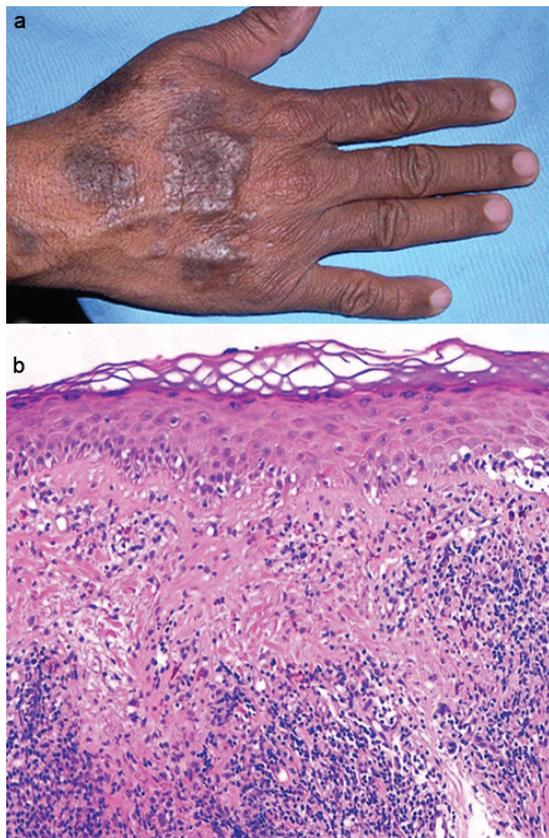


Fig. 2. Case 2. (a) Erythematoviolaceous papular lesions on the wrist and dorsum of the hand. (b) Interface dermatitis pattern with basket-weave hyperkeratosis, slight epithelial atrophy, hypergranulosis, basal epidermal vacuolization and prominent lymphocytic infiltrate at the dermoepidermal junction ($\times 100$).

DISCUSSION

Lichen planus and lichenoid drug eruptions share common histopathological features of lichenoid tissue reaction/interface dermatitis (LTR/IFD) pattern with hallmark vacuolar degeneration/apoptosis of basal epidermal keratinocytes and band-like lymphocytic infiltrate at the dermo-epidermal junction (2). Cases belonging to the clinical spectrum of LTR/IFD arising during anti-TNF- α treatment have been reported previously in rheumatological and dermatological patients and reviewed by Asarch et al. (3), showing localized/generalized as well mucocutaneous and follicular involvement (4). Notably, all three available anti-TNF- α agents (infliximab, etanercept and adalimumab) have been implicated in these reports, suggesting a relevant class-dependent adverse event. The majority of these cases concern patients affected by rheumatoid arthritis and with infliximab as the causative drug, probably due to a longer history of use (5). Consistent histopathology, chronological relationship, exclusion of suspected comedication, clinical remission upon drug withdrawal and recurrence upon drug-rechallenge, as also observed by our department (6), confirm the role of anti-TNF- α

agents as culprit drugs. Moreover, in the second case described above, therapy switching to a different TNF- α antagonist, adalimumab, proved safe, without any recurrence of lichenoid lesions. Other reports describe "psoriasiform" eruptions induced by TNF- α antagonists showing a distinct LTR/IFD histology, as was observed in the first case, further complicating differential diagnosis and therapeutic strategy (7). LTR/IFD is currently viewed as a T-cell-mediated inflammatory disorder, in which destruction of basal epidermal keratinocytes is induced by autoreactive CD8⁺ effector T cells. Recent evidence suggests a prominent role of plasmacytoid dendritic cells (pDCs) in the early phase of LTR/IFD producing type I interferons, such as IFN- α (8). LTR/IFD represents an uncommon type of adverse event of TNF- α -blocking therapy, with an estimated prevalence of one case every 300 patients affected by rheumatoid arthritis (9). The prevalence of LTR/IFD in psoriasis patients, treated with TNF- α antagonist is unknown, and differential diagnosis with psoriasis-flare, drug-induced lupus and other adverse cutaneous events is difficult. As observed in our cases, LTR/IFD can be clinically relevant, necessitating to drug discontinuation and a switch to a different class of TNF- α antagonist or immunomodulatory therapy.

REFERENCES

- Lee H, Song I, Friedrich M, Gauliard A, Detert J, Röwert J, et al. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists. *Br J Dermatol* 2007; 156: 486–491.
- Sontheimer RD. Lichenoid tissue reaction/interface dermatitis: clinical and histological perspectives. *J Invest Dermatol* 2009; 129: 1088–1099.
- Asarch A, Gottlieb AB, Lee J, Masterpol KS, Scheinman PL, Stadecker MJ, et al. Lichen planus-like eruptions: an emerging side effect of tumor necrosis factor-alpha antagonists. *J Am Acad Dermatol* 2009; 61: 104–111.
- Garcovich S, Manco S, Zampetti A, Amerio P, Garcovich A. Onset of lichen planopilaris during treatment with etanercept. *Br J Dermatol* 2008; 158: 1161–1163.
- Vergara G, Silvestre JF, Betlloch I, Vela P, Albares MP, Pascual JC. Cutaneous drug eruption to infliximab: report of 4 cases with an interface dermatitis pattern. *Arch Dermatol* 2002; 138: 1258–1259.
- De Simone C, Caldarola G, D'Agostino M, Rotoli M, Capizzi R, Amerio P. Lichenoid reaction induced by adalimumab. *J Eur Acad Dermatol Venereol* 2008; 22: 626–627.
- Seneschal J, Lepreux S, Bouyssou-Gauthier M, Hélot-Hosten I, Economu A, Dehais J, et al. Psoriasiform drug eruptions under anti-TNF treatment of arthritis are not true psoriasis. *Acta Derm Venereol* 2007; 87: 77–80.
- Meller S, Gilliet M, Homey B. Chemokines in the pathogenesis of lichenoid tissue reactions. *J Invest Dermatol* 2009; 129: 315–319.
- Flendrie M, Vissers WHPM, Creemers MCW, de Jong EMGJ, van de Kerkhof PCM, van Riel PLCM. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. *Arthritis Res Ther* 2005; 7: R666–676.