Case Report

New-Onset Psoriatic Palmoplantaris Pustulosis Following Infliximab Therapy: A Class Effect?

CHRISTIAN HUBERT ROUX, OLIVIER BROCQ, NATHALIE LECCIA, DAMIEN GIACCHERO, VERONIQUE BREUIL, CHRISTINE ALBERT, JEAN LACOUR, CHRISTOPHE PERRIN, and LIANA EULER-ZIEGLER

ABSTRACT. Reports of induction or exacerbation of psoriatic palmoplantaris pustulosis (PPPP) after anti-tumor necrosis factor-α (TNF-α) treatment are few. We describe 2 new cases of PPPP induced by infliximab. In 1999, a total of 442 patients in our department received anti-TNF-α treatment for a variety of chronic rheumatic conditions and were regularly followed. Medical records for 166 given infliximab were retrospectively reviewed for disease [rheumatoid arthritis (RA), spondylarthropathies (SpA) including psoriatic arthritis], disease duration, clinical characteristics, skin side-effects, and use of other potentially relevant medications. PPPP was observed in 2 patients treated with infliximab for symmetrical rheumatoid factor-positive RA; the patients had no personal or family history of psoriasis. In both cases, pustulosis appeared after several months of infliximab administration. There was no clinical, biological, or radiological evidence to support a diagnosis of psoriatic SpA. Both patients fulfilled ACR criteria for RA, and there was no reason to suspect previously unidentified psoriasis. Comorbid RA and psoriasis are unusual, and our patients exhibited a clear link between anti-TNF-α administration and cutaneous lesions, suggesting a direct effect in both cases. The 28 published cases of PPPP induced by anti-TNF-α treatment report lesions that tend towards pustulosis and palmoplantar localization. The mechanisms involved remain elusive. Disappearance of lesions in our second patient when switched to a soluble receptor suggests a molecule-specific side effect, while the literature describing variable reaction to switching anti-TNF agents, and/or their discontinuation and reintroduction, indicates otherwise. Given the rarity of this side effect, its elucidation will require systematic study. (First Release Jan 15 2007; J Rheumatol 2007;34:434–7)

Key Indexing Terms:
ANTI-TUMOR NECROSIS FACTOR-α PSORIATIC PALMOPLANTARIS PUSTULOSIS
RHEUMATOID ARTHRITIS

Recent studies have demonstrated the efficacy of tumor necrosis factor-α (TNF-α) antagonists in the treatment of Th1 phenotype diseases, particularly rheumatoid arthritis (RA), spondyloarthropathies (SpA), psoriatic arthritis (PsA), and cutaneous psoriasis. Tolerance is usually excellent; however, various cutaneous side effects have been described with each anti-TNF agent[1], and several paradoxical reports of psoriasis induction or exacerbation have been published[2,3]. Described cases tend to be pustular, with palmoplantar localization of the lesions.

From the Departments of Rheumatology and Dermatology and the Central Department of Pathology, University Hospital, Nice, France.

C.H. Roux, MD; O. Brocq, MD, Department of Rheumatology; N. Leccia, MD, Central Department of Pathology; D. Giacchero, MD, Department of Dermatology; V. Breuil, MD, Department of Rheumatology; C. Albert, MD; J. Lacour, MD, Department of Dermatology; C. Perrin, MD, Central Department of Pathology; L. Euler-Ziegler, MD, Department of Rheumatology.

Address reprint requests to Dr. C.H. Roux, Rheumatology Department, Hospital l'Archet 1, 242 Avenue de Saint Antoine de Ginestiere, 06200 Nice, France. E-mail: roux101fr@yahoo.fr

Accepted for publication October 13, 2006.

We describe 2 new cases of psoriatic palmoplantaris pustulosis (PPPP) induced by infliximab.

CASE REPORTS

In 1999, anti-TNF-α was used at our institution to treat various chronic rheumatic conditions; all 442 patients treated were followed up regularly. A total of 166 received infliximab[4]. Medical records in this subgroup were reviewed retrospectively to identify the disease (104 had RA and 53 had SpA, including 9 PsA), disease duration, clinical characteristics, skin side effects, and use of disease modifying antirheumatic drugs (DMARD). We identified 2 RA patients who developed PPPP.

Patient 1. Patient 1 was a 42-year-old woman with a 16-year history of severe symmetrical rheumatoid factor-positive RA fulfilling 1989 American College of Rheumatology (ACR) criteria. She did not smoke, and had no personal or family history of psoriasis or endocrine anomalies. She was treated with infliximab 250 mg (3 mg/kg) every 8 weeks with concomitant methotrexate (10 mg/wk) for 30 months without development of antinuclear antibodies (ANA). Although results were good, after 30 months, and 6 weeks following each infliximab infusion, she developed PPPP (Figure 1), which resolved 5 days after the subsequent infusion. Skin biopsy of the sole (Figure 2A, 2B) showed a subcorneal spongiform pustule surrounded by psoriasiform epidermal proliferation characterized by acanthosis, and regularly elongated rete ridges. Immunohistochemistry on paraffin slides was characterized by a CD3+ T cell infiltrate, with no CD20+ B cells. On frozen slides, there was a

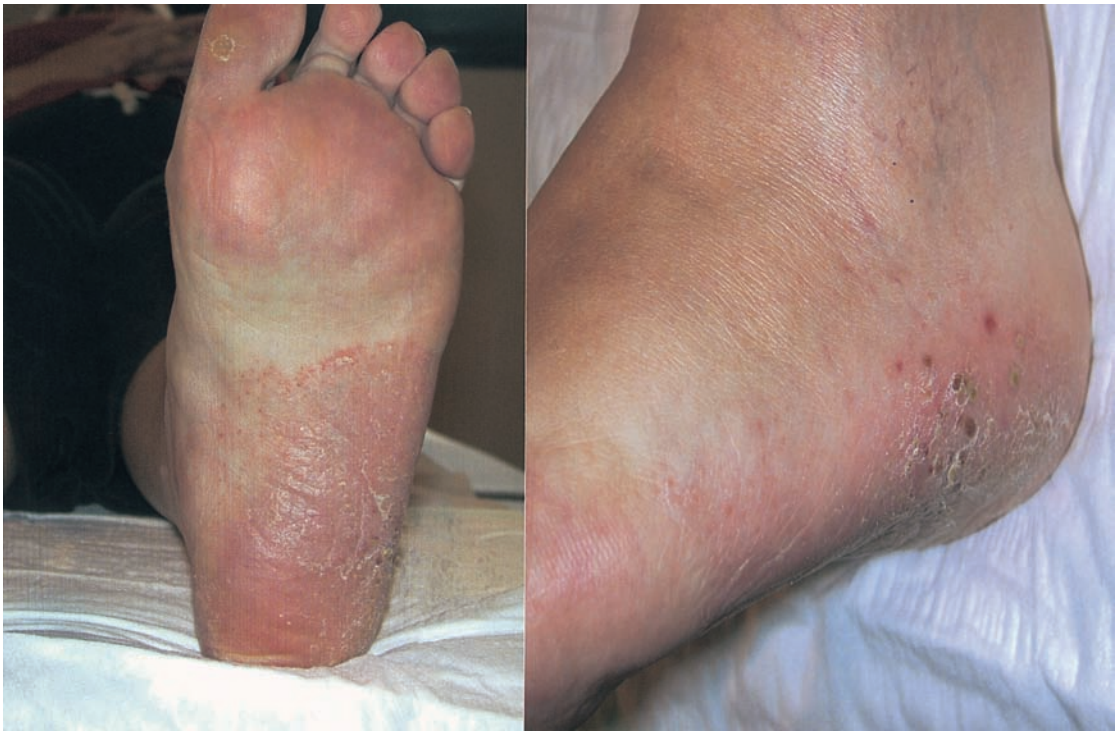

Figure 1. Plantar pustulosis.

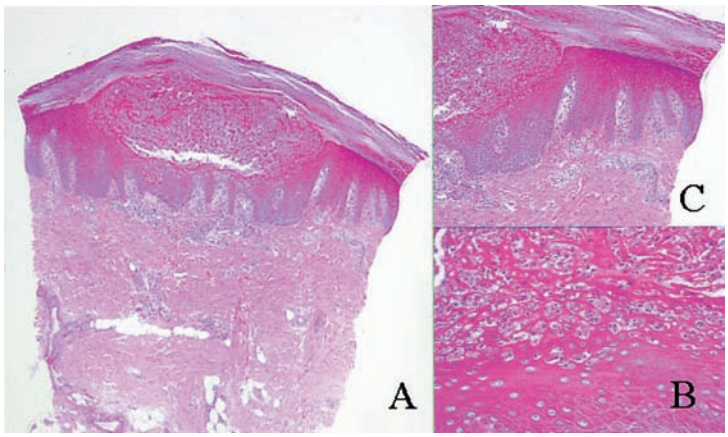

Figure 2. A. Skin biopsy of the sole in Patient 1. A subcorneal spongiform pustule is surrounded by acanthosis and elongated rete ridges (hematoxylin and eosin, magnification ×40). B. Closer view of the pustule, which is formed by collections of neutrophils in the spinous and granular layers (hematoxylin and eosin, magnification ×100). C. Skin biopsy in Patient 2. Large collections of neutrophils with spongiosis in the upper spinous and granular layers (hematoxylin and eosin, magnification ×400).

predominatly CD4+ T lymphocyte infiltrate in the papillary dermis with some CD8+ T lymphocytes. It showed equal numbers of CD4+ and CD8+ in exocytosis in the epidermis. Five months later, infliximab lost efficacy against arthritis and pustulosis, and was discontinued. Subsequent adalimumab was successful as far as the arthritis was concerned, but not the skin manifestations. PPPP persisted at the time of writing.

Patient 2. A 32-year-old woman had a 7-year history of severe symmetrical rheumatoid factor-positive RA fulfilling ACR 1989 criteria. She was a smoker with no personal or family history of psoriasis, and no endocrine anomalies. She was treated successfully with infliximab 150 mg (3 mg/kg) every 8 weeks for 7 months before developing plantaris pustulosis on the soles of her feet, and diffuse erythemato-squamous skin lesions on her legs, arms, and trunk. ANA (1/1280) were present before treatment and increased up to 1/6400 thereafter. Anti-DNA were not present. Skin biopsy of the sole revealed a spongiform subcorneal pustule consisting of neutrophils in the spinous and granular layers (Figure 2C). Immunohistochemistry on paraffin

and frozen slides showed the same results as in the first case. Infliximab was discontinued and etanercept initiated at 25 mg twice a week. The results were excellent, with resolution of both skin lesions and arthritis. At the time of writing, the benefits had persisted for 3 years.

DISCUSSION

Both cases described here involve longstanding rheumatoid factor-positive RA in patients who had no personal or family history of psoriasis. Pustulosis appeared after several months of infliximab treatment. In the first case, infliximab initially had a beneficial effect on arthritis and pustulosis, and subsequent administration of adalimumab was effective with regard to the arthritis, but not the skin symptoms.

Both patients fulfilled ACR criteria for RA with no clinical, radiological, or biological evidence of psoriatic spondyloarthropathy. The diagnosis of PPPP was well documented and supported by skin biopsy findings of parakeratosis, acanthosis, intraepidermal pustulosis, dermal perivascular infiltration, and neutrophil suffusion in the papillar dermis. There was no reason to suspect new-onset psoriasis, and comorbid RA and psoriasis is unusual. Moreover there was a clear temporal link between anti-TNF-α administration and cutaneous lesions in both cases.

To our knowledge, 26 observations have been reported of PPPP induction after anti-TNF-α treatment[5-14], and 2 cases of palmoplantar relapses in patients with SAPHO syndrome[15] (Table 1). PPPP is more frequently seen in smokers: one of our patients was a smoker, and in published cases smoking is mentioned twice[9]. Preexisting psoriasis is mentioned in 3 cases (2 individual and 1 familial)[2] and preexisting pustulosis in 3 other cases[9,13]. In 7 cases no preexisting psoriasis was present[2,3,6,7,9,10]. This is not detailed in other cases, and no lupus-like syndrome is noted. ANA were sometimes detected; indeed, ANA were found in one of our 2 cases prior to treatment and ANA increased after infliximab. Anti-TNF patch tests for ANA were performed in a single report describing induced psoriasis (7 patients) or pustulosis (1 patient)[10], with negative early results and delayed positive results (3 out of 5 patients) in 3 infliximab and 2 etanercept treated patients, respectively. ANA status is not reported for the single pustulosis case. Patch tests were positive in 32–50% of patients with cutaneous drug adverse reactions, and false-positive results were observed. The predictive value of patch tests is unknown[16].

In pustulosis, immunohistochemistry shows a pronounced infiltration of neutrophils and of predominantly CD4+ T cells. Such infiltrate was present in our 2 anti-TNF induced cases, as observed in the single immunochemical study of anti-TNF induced pustulosis[8]. In pustulosis, infiltrating T cells, which

Table 1. Characteristics of reported patients in whom psoriatic palmoplantaris pustulosis developed during anti-TNF therapy.

Authors	Disease	Induced Psoriasis	Anti-TNF	Induced Pustulosis	HLA	ANA
Flendrie[1]	RA	3	Infliximab	1	—	—
Kary[2]	RA	9	Adalimumab			—
			Etanercept	4	DR4 (2)	—
			Infliximab			—
Sfikakis[3]	RA, AS, Behçet	5	Adalimumab			—
			Etanercept	4	—	—
			Infliximab			—
Jarrett[5]	RA	1	Infliximab	1	—	Negative
Baeten[6]	SpA	3	Infliximab	3	B-27 positive (3) in a majority	Positive of patients
Dereure[7]	RA	1	Etanercept	1	—	—
		1	Infliximab	—	—	—
Thurber[8]	Ulcerative colitis	1	Infliximab	1	B-27 negative	Positive (DNA-)
Michaelson[9]	RA	—	Etanercept	6	—	Negative (2)
			Infliximab	—	—	—
Seneschal[10]	AS	8	Etanercept	1	—	—
	RA	—	Infliximab	—	—	—
Zarnitsky[11]	RA	—	Adalimumab	1	—	—
Solau-Gervais[12]	RA	—	—	1	—	—
Djennane[13]	Shulman syndrome	—	Infliximab	1	—	—
Cohen[14]	AS	—	Infliximab	1	B-27 negative (2)	—
Massara[15]	SAPHO syndrome	—	Infliximab	2	—	Negative (2)
Our cases	RA	—	Infliximab	2	—	Positive (1)

RA: rheumatoid arthritis, AS: ankylosing spondylitis, SpA: spondyloarthropathy, ANA: antinuclear antibody.

are strongly positive for CXCL8 and chemokine receptor CCR6, secrete CXCL8 and granulocyte macrophage-colony stimulating factor and could orchestrate neutrophil-rich pathologies such as pustulosis[17].

The mechanisms of anti-TNF induced psoriasis and the reasons for the predominant pattern of pustulosis, which is clinically and genetically distinct from psoriasis vulgaris[18], remain elusive, in particular because several reports suggest that psoriatic pustulosis is an appropriate target for anti-TNF-α therapies[19,20]. The association of PPPP with infliximab, etanercept, and adalimumab suggests a class effect. However, PPPP can present in the same patient in response to different anti-TNF agents[2,9], as in our first case; it can also present in response only to a specific anti-TNF[2,3]. Here, the disappearance of lesions when Patient 2 was treated with a soluble receptor suggests a molecule-specific effect, but the variable outcome in the literature when different anti-TNF agents are discontinued and/or reintroduced indicates otherwise. The rarity of this kind of side effect necessitates systematic study.

REFERENCES

1. Flendrie M, Vissers W, Criemens M, De Jong E, De Kerkhof P, Van Riel P. Dermatological conditions during TNF blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther 2005;7:R666-76. Epub 2005 Apr 4.
2. Kary S, Worm M, Audring H, et al. New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving TNF alpha antagonists. Ann Rheum Dis 2006;65:405-7. Epub 2005 Sep 8.
3. Sfikakis PF, Iliopoulos A, Elezoglou A, Kittas C, Stratigos A. Psoriasis induced by anti-tumour necrosis factor therapy. A paradoxical adverse reaction. Arthritis Rheum 2005;52:2513-18.
4. Brocq O, Roux CH, Albert C, et al. Maintien thérapeutique des 3 anti TNF disponibles, dans la Polyarthrite Rhumatoïde (PR), la Spondylarthrite Ankylosante (SPA) et le Rhumatisme Psoriasique (RP): à propos de 571 prescriptions d'anti TNF chez 442 patients sur une période de 6 ans [abstract]. Rev Rhum 2005;72:918.
5. Jarrett SJ, Cunnane G, Conaghan PG, et al. Anti-tumor necrosis factor alpha therapy-induced vasculitis: cases series. J Rheumatol 2003;30:2287-91.
6. Baeten D, Kruithoff E, Van den Bosch F, et al. Systematic safety follow-up in a cohort of 107 patients treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? Ann Rheum Dis 2003;62:829-34.
7. Dereure O, Guillot B, Jorgensen C, Cohen JD, Combes B, Guilhou J. Psoriatic lesions induced by anti-tumour necrosis factor alpha treatment: 2 new cases. Br J Dermatol 2004;150:506-7.
8. Thurber M, Feasel A, Stroehlein J, Hymes SR. Pustular psoriasis induced by infliximab. J Drugs Dermatol 2004;3:439-40.
9. Michaelson G, Kajermo U, Michaelson A, Hagforsen E. Infliximab can precipitate as well as worsen palmo plantar pustulosis: possible linkage to the expression of tumour necrosis factor alpha in the normal palmar eccrine sweat duct. Br J Dermatol 2005;153:1243-4.
10. Seneschal J, Heliot-Hosten I, Bouysou-Gauthier ML, et al. Eruption psoriasiforme sous anti-TNF alpha: un mécanisme toxidermique? [abstract]. Rev Rhum 2005;72:1009.
11. Zarnitsky C, Bravard P, Godon J, Alcaix D. Pustulose palmaire et plantaire chez une patiente traitée par adalimumab. Rev Rhum 2005;72 Pu 86:1195.
12. Solau-Gervais E, Lebas D, Duquesnoy B, Delaporte E, Flipo R. Cutaneous modifications during anti-TNF therapy in rheumatoid arthritis [abstract]. Ann Rheum Dis 2005;64 Suppl III:458.
13. Djennane S, Oro S, Lévy-Weil FE, Sigal M, Feldman JL. Psoriasis cutané induit par traitement anti-TNF alpha au cours d'une fasciite éosinophile [abstract]. Rev Rhum 2005;72, 10-11, Pu 57:1183.
14. Cohen JD, Bournerias I, Buffard V, et al. Psoriasis induced by tumor necrosis factor alpha antagonist therapy: a case series. J Rheumatol 2007;34:380-5. Epub 2006 Oct 1.
15. Massara A, Cavazzini PL, Trotta F. In Sapho syndrome anti-TNF alpha therapy may induce persistent amelioration of osteoarticular complaints, but may exacerbate cutaneous manifestations. Rheumatology Oxford 2006;45:730-3. Epub 2006 Jan 10.
16. Barbaud A. Drug patch testing in systemic drug allergy. Toxicology 2005;209:209-16.
17. Keller M, Spanou Z, Schaerli P, et al. T cell regulated neutrophilic inflammation in auto-inflammatory diseases. J Immunol 2005;175:7678-86.
18. Asumalahiti K, Ameen M, Suomela S, et al. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmo-plantar pustulosis. J Invest Dermatol 2003;120:627-32.
19. Benoist S, Toksoy A, Brocker EB, Gillitzer R, Gobeler M. Treatment of recalcitrant pustular psoriasis with infliximab: effective reduction of chemokine expression. Br J Dermatol 2004;150:1009-12.
20. Schmick K, Grabbe J. Recalcitrant generalized pustular psoriasis: rapid and lasting therapeutic response to antitumour necrosis factor alpha antibody (infliximab) [letter]. Br J Dermatol 2004;150:367.