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Letter to the Editor

Certolizumab Pegol-induced Palmoplantar Pustulosis: A Case Report and Review of the Literature☆

Pustulosis palmoplantar inducida por certolizumab pegol: presentación de un caso y revisión de la literatura

Dear Editor,

The biological drugs that target tumour necrosis factor α (TNFα) are now widely used to treat rheumatoid arthritis (RA) and other immunomediated inflammatory diseases. Although they have been shown to be highly effective and to have a good safety profile,[1] they are also associated with adverse cutaneous events, including psoriasis and psoariasiform lesions.[2] We present a patient diagnosed RA who developed palmoplantar pustulosis (PPP) during treatment with certolizumab pegol (CZP), and we also review the published cases of psoriasis induced by this drug.

A 57 year-old male with a history of diabetes mellitus and arterial hypertension was diagnosed RA at the age of 50 years-old due to his polyarthritis in the small joints of the hands, raised acute phase reagents and positivity for rheumatoid factor and anti-cyclic citrullinated peptide antibodies. He was treated at first with methotrexate (maximum dose 20 mg/week, subcutaneous), with clinical improvement and good tolerance. However, after 5 years he underwent gradual worsening of the inflammatory symptoms in the hands and persistently high levels acute phase reagents (disease activity measured by DAS28: 5). Due to this it was decided to add CZP (subcutaneous 200 mg every 2 weeks), achieving a good response in the joints and analytical results within the first 2 months. After 3 months of anti-TNFα treatment he visited the emergency department due to a sudden outbreak of converging and painless millimetrical pustular lesions on the palms and soles of the feet (Fig. 1), with no signs of infection or lesions in other locations. Biopsy of a palm lesion was histopathologically compatible with PPP. CZP was withdrawn, but methotrexate was maintained, starting topical corticoid therapy with betamethasone cream. The latter was subsequently changed to clobetasol cream with occlusive bandages and laser sessions, and the lesions disappeared completely 4 months after suspending the anti-TNFα. The patient remained in remission after a 6-month observation period, continuing treatment only with subcutaneous methotrexate 25 mg/week, without the need to recommence the biological treatment.

The appearance of psoriasis *de novo* or worsening of pre-existing psoriasis is an AE associated with all anti-TNFα drugs, and it may occur at any time (from days until years after the start of treatment), without any variations according to sex or age.[2,3] Although it has been described in almost all of the diseases treated with anti-TNFα, up to 75% of cases correspond to inflammatory rheumatological disease.[2] A recent meta-analysis that included 216 cases of *de novo* psoriasis induced by anti-TNFα found the following frequency for each of the following drugs: infliximab 62%, adalimumab

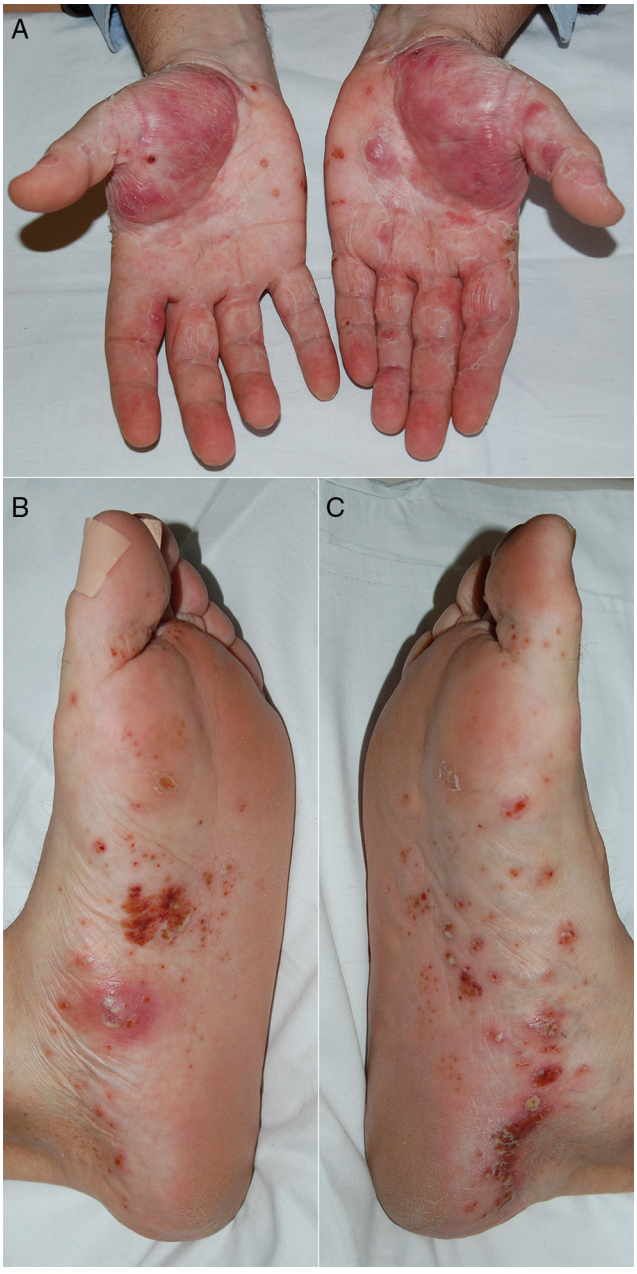

Fig. 1. Appearance of pustular lesions, mainly located on the thenar eminences of both palms (A) and on the medial zone of the soles of the right (B) and left (C) feet, showing a tendency to converge and leaving wide zones of flaking and erythema on the hands.

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Table 1
Characteristics of the Patients With Certolizumab-induced Psoriasis.

Study	Age (years)	Sex	Base disease	PH/FH of psoriasis	Previous treatments	CZP treatment pattern	Type of psoriasis	Time to appearance of induced psoriasis	Evolution
Shelling et al.[4]	78	M	RA	No/no	MTX, ETN	400 mg every 2 weeks, sc	PPP	10 weeks with ETN 6 weeks with CZP	Improvement following the suspension of CZP and high power topical corticoid treatment
Koizumi et al.[5]	71	W	RA	No/no	MTX, IFX	200 mg every 4 weeks, sc	PPP → GPP	122 days until the development of PPP 157 days until the development of GPP	No response following suspension of CZP and topical corticoid treatment Rapid improvement of the lesions (one week) with oral etretrinate (20 mg/day), but without completely disappearing
Eickstaedt et al.[6]	14	M	CD	No/no	IFX	ND	PsoP	29 months with IFX 3 months with CZP	Remission of the first outbreak following suspension of IFX topical treatment with triamcinolone and calcipotriene and dressings with acetic acid Remission of the second outbreak after suspension of CZP and topical treatment with hydrocortisone
	17	W	CD	No/no	IFX	ND	PsoP	6 months with IFX Unspecified time with CZP	Remission of the first outbreak after suspension of IFX and topical treatment with triamcinolone and hydrocortisone Remission of the second outbreak after suspension of CZP and treatment with MTX and topical hydrocortisone
	18	W	CD	No/no	ADA	ND	PsoP	Unspecified time with ADA 6 months with CZP (+MTX)	Remission of the first outbreak after suspension of ADA and topical treatment with hydrocortisone and betamethasone Remission with topical treatment with flucinolone and calcipotriene
Fischer et al.[7]	38	M	CD	PsoP/no	ND	ND	PsoG	One week until development of PsoG	Remission after suspension of CZP and topical treatment with triamcinolone Start of IFX and oral PDN for CD, no recurrence of PsoG
Mocciaro et al.[8]	42	W	CD	No/no	MTX, IFX	400 mg every 4 weeks, sc	PPP + PsoP	29 weeks until development of PPP	No response after suspension of CZP and treatment with topical corticoids Complete remission of the lesions with CSA (3 mg/kg/day) and oral acitretrin (10 mg/day)
Klein et al.[9]	26	W	CD	No/no	ND	ND	PPP + PsoG	4 months until the development of PPP	Initial improvement in pustular lesions with suspension of CZP and oral PDN 30 mg/day Improvement of PsoG with MTX (25 mg/week), that had to be changed to 6-MP Recurrence of PPP that improved with UBV phototherapy and topical treatment with betamethasone and calcipotriene
Protic et al.[10]	ND	ND	CD	No/no	ND	ND	NE	ND	ND
The current case	57	M	RA	No/no	MTX	200 mg every 2 weeks, sc	PPP	3 months until development of PPP	Remission after suspension of CZP and topical treatment with betamethasone and clobetasol and laser sessions

ADA: adalimumab; FH: family history; PH: personal history; RA: rheumatoid arthritis; CSA: cyclosporine A; CZP: certolizumab pegol; CD: Crohn's disease; ETN: etanercept; M: man; IFX: infliximab; W: woman; MTX: methotrexate; ND: no available data; NE: not specified; GPP: generalised pustular psoriasis; PPP: pustulosis palmoplantar; PsoG: psoriasis *guttata*; PsoP: plaque psoriasis; sc: subcutaneous; UBV: ultraviolet B light.

21.8%, etanercept 14.4%, CZP 1% and golimumab 0.5%.[3] Rather than reflecting any difference between these drugs, this may be due to the higher number of patient-years of exposure to the first anti-TNFα approved, in comparison with CZP and golimumab, and it is now considered to be a class effect of these drugs.[2,3]

In our review of the literature (PubMed) we found 9 cases of CZP induced psoriasis, 2 in RA and 7 in Crohn's disease (Table 1). The cases which occurred in RA corresponded to PPP; in the first of these it was a recurrent AE (the first event after etanercept),[4] while in the second it appeared *de novo* and progressed to generalised pustular psoriasis (GPP).[5] CZP was withdrawn in both cases and after dermatological treatment the patients showed good clinical evolution of the lesions. All of the cases which arose in Crohn's disease were *de novo* (3 with CZP as the first anti-TNFα and 3 in which it was the second) and the types of psoriasis they had were: plaque psoriasis (3),[6] *guttata* psoriasis (1),[7] PPP + plaque psoriasis (1),[8] PPP + *guttata* psoriasis (1)[9] and one unspecified type (1).[10] In 5 cases CZP was suspended, 4 cases had a good response to topical corticoid therapy and 2 cases also required photochemotherapy and acitretrin.

The types of anti-TNFα-induced psoriasis described the most often in the literature are: plaques 44.8%, PPP 36.3%, GPP 10.9% and *guttata* 8%.[3] The high frequency with which PPP occurs in patients treated with anti-TNFα in comparison with the general population (an incidence of 0.12%) suggests that this is a specific AE of these drugs. Although suspension of the treatment is not always indispensable, severe forms such as PPP and GPP may respond better if the anti-TNFα is withdrawn.[6]

To conclude, CZP may be associated with the development of induced psoriasis, as is the case with other anti-TNFα drugs, regardless of their indication, and PPP is one of the most frequent forms of presentation.

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