

Nonpigmenting fixed drug eruption as a possible abortive variant of toxic epidermal necrolysis: immunohistochemical and serum cytokine analyses

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Summary

Nonpigmenting fixed drug eruption (NPFDE) is clinically indistinguishable from Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) in its initial presentation. The traditional paradigm that epidermal changes are absent in NPFDE cannot be easily reconciled with the clinical resemblance to SJS/TEN. We therefore investigated whether NPFDE is pathogenetically different from pigmented FDE (PFDE) or SJS/TEN and which factors are responsible for the lack of hyperpigmentation. NPFDE lesions before challenge were characterized by larger numbers of CD8+ intraepidermal T cells associated with a paucity of melanocytes, compared with those in PFDE. Very high levels of serum interleukin (IL)-10 were noted after clinical challenge. We conclude that NPFDE is a clinical syndrome with heterogeneous histological expression. NPFDE with epidermal involvement may be an abortive form of SJS/TEN, in which progression to TEN can be prevented by IL-10.

Nonpigmenting fixed drug eruption (NPFDE) can have multiple variants, all characterized by symmetrical, well-circumscribed, erythematous plaques resolving without pigmentation. It is clinically indistinguishable from Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) in its initial presentation.¹ Additionally, a localized form of NPFDE has also been reported.² Because of the clinical similarity between these conditions, it has been suggested that the multiple variant represents the mild end of the spectrum of SJS/TEN. However, severe epidermal damage is absent in NPFDE, which seems inconsistent with this theory. Thus, it remains to be determined whether the multiple variant is a subtype of the FDE spectrum or an abortive variant of the TEN spectrum. We investigated lesions in

a patient with NPFDE, which were initially thought to represent an early stage of TEN, and compared the results with lesions of pigmented FDE. We also measured the time course of serum cytokine levels sequentially obtained from this patient before and after clinical challenge.

Report

A 69-year-old woman presented with widespread, erythematous and Nikolsky-positive bullous lesions with fever and polyarthralgias (Figs 1a,b). She had noted the rapid appearance of the eruption 6 h after taking mefenamic acid. An initial presumptive diagnosis was of SJS/TEN or NPFDE. The patient recalled two previous similar eruptions involving similar areas after ingestion of mefenamic acid in the past. A biopsy specimen showed more severe epidermal damage than in PFDE, and a diagnosis of NPFDE was made.

Six weeks later, the patient underwent an oral challenge test with one-tenth (50 mg) of a single

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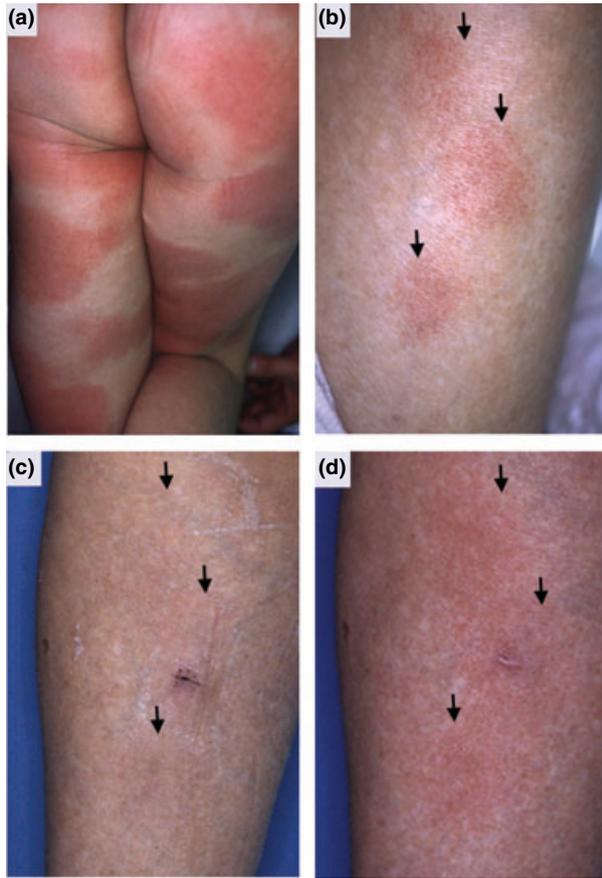


Figure 1 At onset, (a) large, well-demarcated erythematous areas on the buttocks and upper legs, and (b) erythematous plaques on the left lower leg were seen (arrows). (c) Six weeks later, the previously involved sites are barely recognized by faint residual pigmentation and a biopsy scar (arrows). The faint pigmentation faded completely 2 months later. (d) Three hours after oral rechallenge, erythematous lesions appeared at the previously involved sites (arrows).

therapeutic dose. At this time, the previous NPFDE lesions were clinically normal (Fig. 1c). After ingestion of the drug, erythematous plaques appeared in exactly the same sites as the previous lesions (Fig. 1d).

A brief description of the lymphocyte subsets in this patient has been previously reported.³ Anti-CD8 and anti-Melan-A (melanocyte differentiation antigen) (both from Dako, Glostrup, Denmark) were used to identify intraepidermal CD8+ T cells and melanocytes, respectively. The number of intraepidermal CD8+ T cells along the basal layer in the resting NPFDE lesions was found to be higher than those in the resting PFDE lesions (NPFDE, 81.5 ± 10.7 cells/mm, $n = 4$; PFDE, 29.0 ± 3.7 cells/mm, $n = 11$, $P < 0.01$) (Figs 2a,b). In contrast, melanocytes and dermal melanophages in the NPFDE lesions were dramatically

decreased in number compared with those in PFDE lesions (melanocytes in 6 NPFDE lesions 5.8 ± 0.5 cells/mm and in 9 PFDE lesions, 17.9 ± 2.2 /mm $P < 0.01$; dermal melanophages in 8 NPFDE lesions 30.0 ± 12.3 /mm² and in 11 PFDE lesions 151.3 ± 26.5 /mm², $P < 0.01$) (Figs 2c,d). Thus, the lack of pigmentation after resolution in NPFDE is more likely due to the paucity of dermal melanophages resulting from the dramatic decrease in melanocyte number in the resting lesions before challenge, rather than to the absence of epidermal changes.

Serum concentrations of tumour necrosis factor (TNF)- α , interferon (IFN)- γ , interleukin (IL)-6, IL-8 and IL-10 in relation to the clinical variables are shown in Fig. 3. On first admission, marked increases in IFN- γ and IL-6 and a moderate increase in TNF- α were noted. IFN- γ and IL-6 levels rapidly fell on discontinuation of the causative drug. Three hours after challenge with the causative drug, marked increases in TNF- α and IL-8 were seen. The decrease in IL-8 levels at 5.5 and 7 h was associated with a rise in the IL-6 and IL-10 levels.

In this study, melanocytes in the NPFDE lesions were markedly decreased in number compared with those in the PFDE lesions, and this decrease was reflected in the paucity of dermal melanophages in the NPFDE and PFDE lesions have not previously been quantitatively evaluated. As the number of intraepidermal CD8+ T cells was inversely increased in the basal layer of the resting NPFDE lesions, expansion of these CD8+ T cells with a tendency toward a basal location similar to melanocytes would be expected, and would be related to the decrease in melanocyte number. However, a small number of melanocytes also persisted despite the abundance of CD8+ T cells in the resting NPFDE lesions, which is different to the findings in vitiligo,⁴ indicating that CD8+ T cells residing in the NPFDE lesions may not be so highly functional as those in vitiligo lesions. Given the variation in the number of intraepidermal CD8+ T cells and melanocytes in the resting lesions of NPFDE and PFDE, it appears likely that the frequency, functional activity and cytokine expression patterns of intraepidermal CD8+ T cells residing in the lesions cause variability in the clinical picture and histological patterns. It is possible therefore that the multiple variant of NPFDE as shown in this case could be seen as an intermediate condition between PFDE and SJS/TEN, as CD8+ T cells with a similar phenotype to those in the resting NPFDE lesions have also been

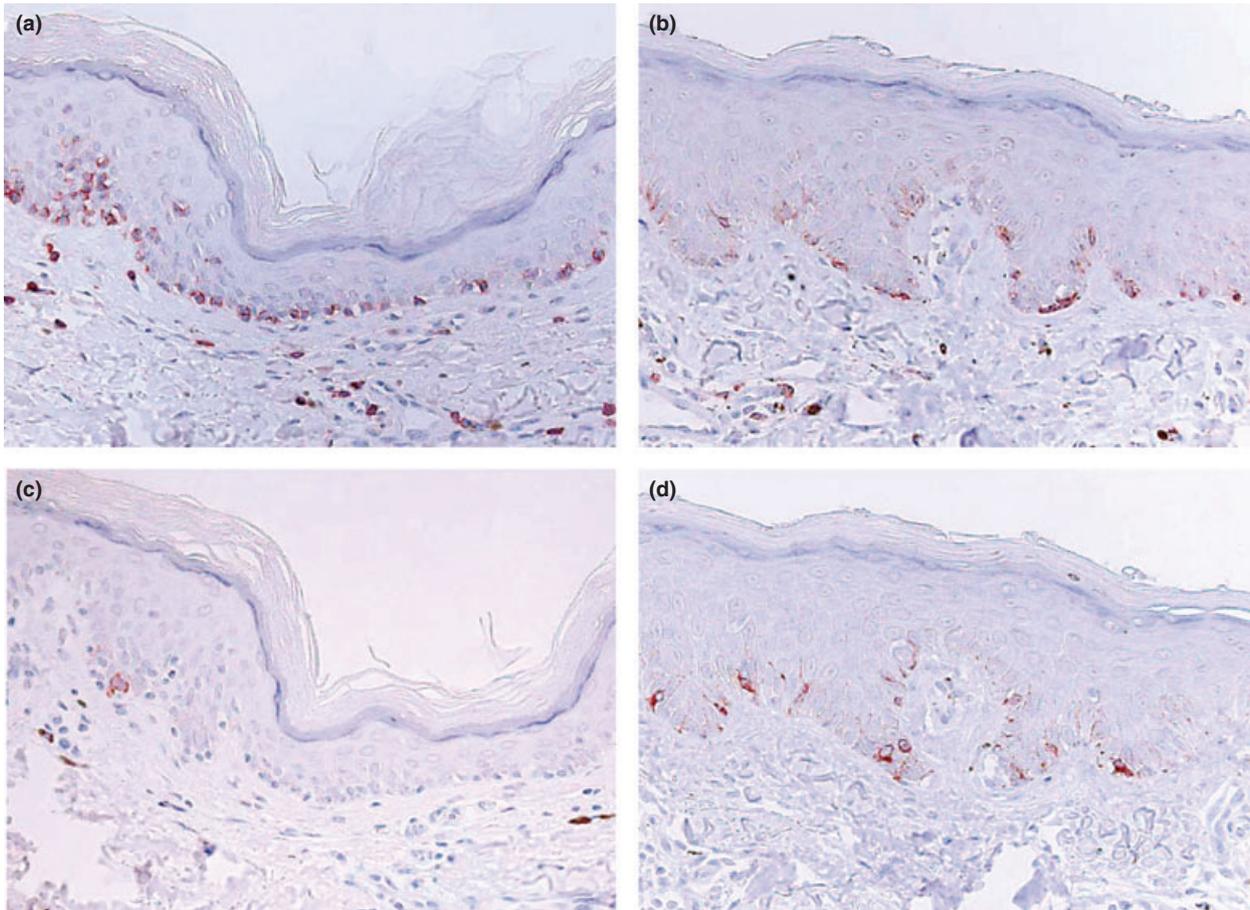


Figure 2 The distribution patterns of (a,b) intraepidermal CD8+ T cells and (c,d) melanocytes in (a,c) the resting nonpigmenting fixed drug eruption lesion and (b,d) the corresponding pigmenting fixed drug eruption lesion in a representative case. Biopsy specimens were obtained from the resting lesions before oral rechallenge. Both intraepidermal CD8+ T cells and melanocytes are predominantly located in the basal layer. Anti-CD8 and anti-Melan-A were used to identify intraepidermal CD8+ T cells and melanocytes, respectively (original magnification, $\times 132$).

found in blister fluid from patients with TEN.⁵ The existence and pathogenesis of a multiple variant of NPFDE clinically and histologically mimicking TEN needs verification in studies with a large number of patients.

The results presented in this study have important implications for factors that may serve to prevent disease progression to TEN. IL-10 levels at various time points showed a clear-cut inverse relationship with the corresponding proinflammatory cytokine levels. In view of the action of IL-10 on immune responses,⁶ increased levels of circulating IL-10 during the development of drug eruptions could reflect an appropriate response that serves to protect tissues from destructive autoimmune attack by activated intraepidermal CD8+ T cells, and the relative balance between IL-10 and

proinflammatory cytokines in diseased tissue would influence whether the inflammation progresses to the fatal outcome or is suppressed.

A multiple variant of NPFDE with systemic symptoms mimicking SJS/TEN in a useful disease model in which to study the mechanism whereby excessive activation of CD8+ T cells can be prevented in NPFDE, although it would be premature to conclude that NPFDE is an abortive form of TEN. Our data provide one potential explanation for why drug-induced immune responses in NPFDE resolve spontaneously upon discontinuation of the causal drug despite the clinical and histological resemblance to TEN; and indicate the clinical usefulness of monitoring levels of various cytokines in predicting the prognosis of drug eruptions.

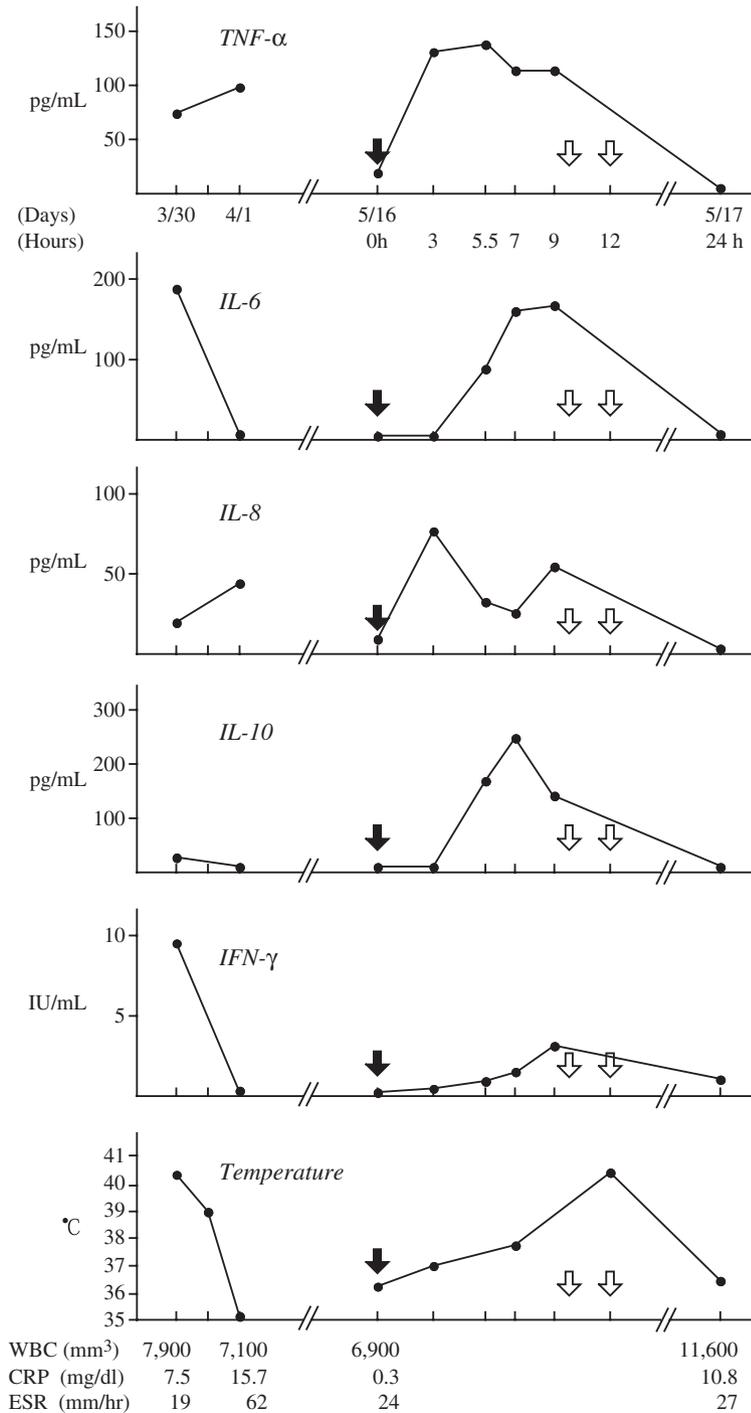


Figure 3 Representative kinetics of serum tumour necrosis factor (TNF)- α , interleukin (IL)-6, IL-8, IL-10 and interferon (IFN)- γ levels in relation to clinical variables at the patient's initial presentation and before and after clinical challenge with the causative drug. Closed arrows indicate the start of the oral rechallenge test; open arrows indicate the point at which systemic corticosteroid was taken to relieve the symptoms. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells.

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References

- Shelley WB, Shelley ED. Nonpigmenting fixed drug eruption as a distinctive reaction pattern. Examples caused by sensitivity to pseudoephedrine hydrochloride and tetrahydrozoline. *J Am Acad Dermatol* 1987; **17**: 403-7.

- 2 Benson PM, Giblin WJ, Douglas DM. Transient, nonpigmenting fixed drug eruption caused by radiopaque contrast media. *J Am Acad Dermatol* 1990; **23**: 379–81.
- 3 Teraki Y, Kokaji T, Shiohara T. Expansion of IL-10 producing CD4+ and CD8+ T cells in fixed drug eruption. *Dermatology* 2006; **213**: 83–7.
- 4 Wijngaard R, Wankowicz-Kalinska A, Le Poole C *et al.* Local immune response in skin of generalized vitiligo patients. *Lab Invest* 2000; **80**: 1299–309.
- 5 Cleach LL, Delaire S, Boumsell L *et al.* Blister fluid T lymphocytes during toxic epidermal necrolysis functional cytotoxic cells which express human natural killer (NK) inhibitory receptors. *Clin Exp Immunol* 2000; **119**: 225–30.
- 6 Maurer M, Seidel-Guyenot W, Metz M *et al.* Critical role of IL-10 in the induction of low zone tolerance to contact allergens. *J Clin Invest* 2003; **112**: 432–9.