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Interleukin-1-beta, Interleukin-6, and Interferon-gamma in Suction Blister Fluids of Involved and Uninolved skin and in Sera of Psoriatic Patients

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Interleukin-1-beta (IL-1-beta), Interleukin-6 (IL-6) and Interferon-gamma (IFN-gamma) were measured by enzyme immunoassay (EIA) methods in blister fluids (BFs) obtained from both involved (ISBF) and non-involved skin (USBF) and in sera from 14 psoriastic patients. The same determinations were carried out in 14 sera and in 5 suction blister fluids from 14 normal subjects. IL-6 was always detectable in all skin fluids and in 3 psoriasis sera. IL-1-beta was measured only in 5 ISBFs and in 5 sera from the same patients. IFN-gamma was preasent in 11 ISBFs, in 5 USBFs and in 5 sera. The analysis of the levels found in the samples shows: 1) a local production of these cytokines, 2) the presence of detectable amounts of IL-6 and IFN-gamma in USBFs, and 3) a significant correlation between the IL-6 levels in the ISBFs and erythema score. ***Key words: psoriasis; blister fluids; IL-6; IL-1-beta and IFN-gamma.***

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Recent investigations emphasize the importance of the interaction of different cytokines in substaining the two main features of psoriatic lesions, viz. inflammation and kerationocyte hyperproliferation (1). In this context, we studied the presence in vivo of Interleukin-1-beta (IL-1-beta), Interleukin-6 (IL-6) and Interferon-gamma (IFN-gamma) in the sera and blister fluids (BFs) obtained from a group of 14 psoriatic patients.

PATIENTS AND METHODS

Fourteen patients with active psoriasis (13 females and 1 male, median age 41, range 15–72 years) and 14 healthy volunteers (12 females and 2 males, median age 43, range 21–50 years) were studied. Of the 14 psoriatic patients, 12 were affected with plaque-type psoriasis, 1 with suberythrodermic psoriasis and 1 with pustular psoriasis. The median Psoriasis Area and Severity Index (PASI) of 13 patients was 11.4; range 3.0–40.5. The patients were untreated for at least 10 days before enrolment. Suction blisters were obtained both from lesional skin (ISBFs) (plaque 3–5 cm in diameter or edge of larger plaques) or unaffected skin (USBFs) (10–15 cm from the lesion) in all patients and from the skin (NSBFs) in 5 og 14 controls, by the Kiistala method (2). Serum samples were obtained from all the patients and controls studied. Methods and technical data are listed in the Table I.

Statistical analysis

The results were expressed as medians and ranges. Accordingly, statistical comparisoons were calculated by non-parameterical methods: Kruskal-Wallis or χ^2 or Spearman Rank correlation tests were used, as necessary.

RESULTS

The IL-1-beta, IL-6, and IFN-gamma levels in BFs and sera from psoriatic patients and controls are presented in Fig. 1. IL-1-beta was detected in ISBFs in 5 out of 14 patients (median 121.5 pg/ml; range 70.4–190.9), and in the corresponding sera (median 15.4 pg/ml; range 7.5–45.5). IL-1-beta levels were consistently higher (8-fold) in the BFs than in the serum samples (Fig. 1a), with a significant direct mutual correlation ($r = 0.96$, $p = 0.006$). No IL-1-beta was detected in the USBFs or in the NSBFs. None of the normal sera had detectable amounts of IL-1-beta. IL-6 was consistently found in the ISBFs and USBFs as well as in BFs of healthy volunteers. As shown in Fig. 1b, the IL-6 levels in the ISBFs were significantly higher (median 1682.5 pg/ml; range 267–12168) than those in psoriatic USBFs (median 120.5 pg/ml; range 7.0–484.4; $p = 0.00002$) or BFs of normal skin (median 10 pg/ml range 7.0–11.0; $p = 0.005$). IL-6 levels in the USBFs were also significantly higher than those in NSBFs ($p = 0.002$). Only 3 of the 14 patients had detectable amounts of IL-6 in their sera (median 72.3 pg/ml range 4.3–230.0). None of the normal sera was positive. A direct correlation between the IL-6 levels in ISBFs and the erythema score was found ($r = 0.63$; $p = 0.01$). IFN-gamma was detected in 11 of the 14 ISBFs (median 0.04 IU/ml; range 0.02–2.94), while lower levels (median 0.03 IU/ml range 0.02–0.05) were found in 5 of the 14 USBFs. Furthermore, 5 of 14 patients had detectable IFN-gamma amounts (Fig. 1c) in their sera (median 0.03 IU/ml; range 0.02–0.05). Normal subjects invariably had undetectable IFN-gamma both in skin BFs and in their sera. The frequency of subjects positive for IFN-gamma in ISBFs differed from that of USBFs or normal skin controls (χ^2; $p = 0.02$; χ^2; $p < 0.05$ respectively). Only 3 of 14 patients had IFN-gamma simultaneously detectable both in the sera and in the ISBFs and USBFs. Patients with high IL-1-beta and IFN-gamma levels in ISBFs corresponded mainly to those with the highest IL-6 concentrations (not shown).

Table I

Test	Producer	Method	Sensitivity	Sample (µl)	DIL
Serum					
IL-1-beta	Medgenix	ELISA	3 pg/ml	100	1/1
IL-6	Medgenix	ELISA	3 pg/ml	200	1/1
IFN-gamma	Medgenix	ELISA	0.2 IU/ml	50	1/1
Fluid					
IL-1-beta	Medgenix	ELISA	15 pg/ml	20	1/5
IL-6	Medgenix	ELISA	15 pg/ml	20	1/5
IFN-gamma	Medgenix	ELISA	0.2 IU/ml	50	1/1

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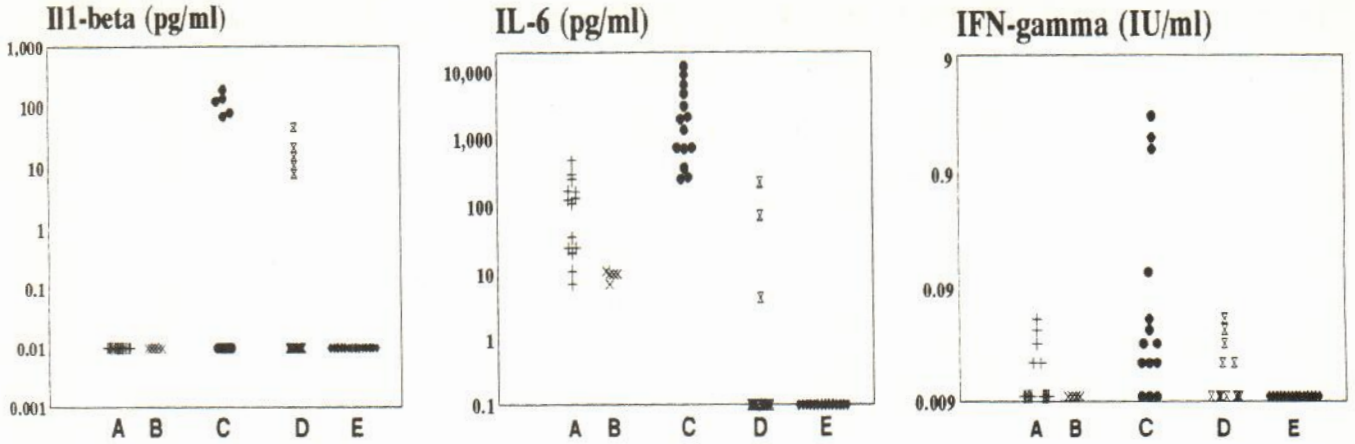

A = uninvolved skin; B = normal skin; C = involved skin; D = psoriasis serum; E = control serum.

DISCUSSION

The higher IL-1-beta levels in the BFs than in the sera confirm the local production of this cytokine at the lesional site. The direct correlation between BFs and serum levels of IL-1-beta may reflect its passage from the skin to the bloodstream. IL-1-beta is present in some ISBFs. Another study failed to detect IL-1-beta in ISBFs found overexpressed on the plasma membrane and in the intracellular compartment of epidermal cells from psoriatic-involved skin (3). This discrepancy may have been due to the different sensitivity of the assays used. At the present time, the role of IL-1-beta in the pathogenesis of psoriasis remains controversial even if an activation of lymphomonocytic cells (4, 5) has been indicated. IL-6 is a pleiotropic cytokine with a prominent pro-inflammatory activity; moreover, it has been shown to stimulate keratinocyte growth '*in vitro*' (6, 7). Interestingly, we could detect significant IL-6 levels in BFs derived either from involved and uninvolved psoriatic skin, or from normal skin. Significantly smaller IL-6 amounts were detected in psoriatic USBFs than in ISBFs, *al* though larger than in normal healthy skin. This finding could be important as it could be speculated that the pathogenetic mechanisms of psoriasis are activated, even to a lesser extent, also in apparently normal skin. Moreover, a direct correlation was found between the IL-6 levels in psoriatic ISBFs and the grade of erythema, suggesting a possible cause-effect phenomenon. Prens et al., using a different methodology, found no significant IL-6 levels in USBFs and in the normal skin (3). Differently from Grossman et al. (7), we detected IL-6 only in the sera of 3 of 14 patients. This disparity could also be due to the different methods employed, i.e. ELISA vs bioassay. The role of IFN-gamma in the pathogenesis of psoriasis is currently being investigated. This cytokine appears to possess many pro-inflammatory properties (8). Furthermore, IFN-gamma has been shown to act directly on keratinocytes to produce TGF-alpha (9). This latter can stimulate its own proliferation in an autocrine/paracrine manner (10). In our study, IFN-gamma could be detected in psoriatic ISBFs (78.5%), in USBFs (35%) and also in patients' sera (35%). In this regard, there are several disparities in the literature (11, 12). As reported for IL-6, some of the USBFs showed detectable IFN-gamma levels. The data provided herein confirm the presence of IL-1-beta, IL-6 and IFN-gamma concomitantly in lesions of a limited number of psoriatic patients. These individuals have the highest levels of IL-6, which seems to play a crucial role in the pathogenesis of psoriasis.

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