

CLINICAL REPORTS

Squamous Cell Carcinoma-related Antigen (SCCr-Ag), sICAM-1 and β 2-Microglobulin are Useful Markers of Disease Activity in Psoriasis

O. DE PITÀ¹, A. FREZZOLINI¹, A. CIANETTI³, G. DE SANCTIS², L. FONTANA² and V. BOTTARI²

¹Department of Immunodermatology, Istituto Dermatologico dell'Immacolata, IDI-IRCCS, ²Department of Internal Medicine, Chair of Allergy and Clinical Immunology and ³Laboratory Unit San Camillo Hospital, Rome, Italy

Several published studies suggest the involvement of immune and inflammatory factors in psoriasis. We recently demonstrated that the number of circulating ICAM-1 + lymphocytes and the levels β 2-microglobulin are useful parameters in monitoring the activity of the disease. In this study we investigated serum levels of SCCr-Ag in 24 patients with psoriasis in order to determine whether this antigen is a marker of disease activity. Our results demonstrated high serum levels of SCCr-Ag, IL-2, sIL-2R, sCD4, sCD8, sICAM-1 and β 2-microglobulin in the acute phase of psoriasis. Furthermore, we found a positive correlation of SCC with TBSA, PASI score, sICAM-1 and β 2-microglobulin. These data demonstrate that serum levels of SCCr-Ag depend on the severity of the disease and correlate with both immunological and inflammatory markers of disease activity. We suggest that expression of SCCr-Ag may be induced by cytokines in the microenvironment of psoriatic lesions, suggesting that SCCr-Ag may play a role in the inflammatory process. **Key words:** psoriasis; immunological markers; inflammatory markers.

(Accepted October 5, 1998.)

Acta Derm Venereol (Stockh) 1999; 79: 132–135.

O. De Pità, Department of Immunodermatology, Istituto Dermatologico dell'Immacolata, Via Monti di Creta, 104 IT-00167 Rome, Italy.

Psoriasis is a chronic inflammatory skin disease of undefined origin in which the immune system seems to play a crucial role. The involvement of immune and inflammatory factors has been suggested by the presence of activated T-cells both in the peripheral blood and in psoriatic skin lesions and by the intervention of cytokines in the inflammatory process (1–11). These data suggest that psoriasis is not merely a cutaneous illness, but that systemic factors are involved in the disease. Thus we have recently focused our attention on some systemic immunological and inflammatory parameters useful in monitoring of the disease activity. We have demonstrated that the levels of circulating ICAM-1 + lymphocytes correlate with cutaneous involvement, while persistence of some cellular and soluble immunological activation markers was observed in apparently normal skin (12, 13). Recently, some authors have reported high serum levels of squamous cell carcinoma related antigen (SCCr-Ag), a neoplastic marker specifically raised in squamous cell carcinoma of the cervix, lung and oesophagus (14), in dermatological diseases such as senile erythroderma following eczema (15) and psoriasis (16). Furthermore, positive immunohistochemical staining for SCCr-Ag monoclonal

antibody was detected in the skin biopsy of the same patients (17). The significance of this finding remains controversial; it has been suggested that SCCr-Ag may be a marker of erythroderma (15) or may be related to serine proteinase activation occurring in psoriasis (16). In this study we investigated serum levels of SCCr-Ag in a group of psoriatic non-erythrodermic patients in the acute and remission phases of the disease in order to verify whether SCCr-Ag is a useful marker of disease activity and whether there is any correlation with other immunological parameters.

MATERIALS AND METHODS

Patients

A total of 24 consecutive patients (15 males and 9 females), age range 42–61, with psoriasis vulgaris (PV) were evaluated in the acute phase. A group of the patients were also studied in the remission phase. Patients were investigated in order to exclude internal malignancy and cutaneous carcinoma. Remission was obtained after 15 days of topical therapy alone (corticosteroids in association with vitamin D3 and emollient cream). Their PASI (Psoriasis Area and Severity Index) score ranged from 3.5 to 12.5 (median 9.5). Patients were also analysed for the extent of cutaneous involvement (Total Body Surface Area, TBSA) (range 15–75%, median 35). As controls, we used blood samples from 20 healthy donors with a similar age and sex distribution, processed at the same time as those of the patients.

SCCr-Ag and CYFRA

SCCr-Ag levels were determined using a monoclonal antibody in an IRMA assay according to the manufacturer's instructions (Abbott, Divisione Diagnostici, Rome, Italy). As a control, soluble cytokeratin 19 fragment (CYFRA) was measured in the same samples, using a specific monoclonal antibody for cytokeratin 19 in an IRMA assay according to manufacturing instructions (Cis-Biointernational, Gif-sur-Yvette, France). Samples were tested in duplicate; intra- and inter-assay variability never exceeded 5%.

Cytokines and soluble factors

Enzyme-linked immunosorbent assay (ELISA) test kits with specific murine MoAb-coated polystyrene microwells were used to detect serum levels of IL-2 (R & D Systems, Minneapolis, MN, USA), sIL-2R, sCD4, sCD8 (T-cell Diagnostics, Inc., Cambridge, MA, USA), sICAM-1 (R & D Systems, Minneapolis, MN, USA) and β 2-microglobulin (Farnos Diagnostica, Finland). All samples and standards were assayed in duplicate.

Statistical analysis

Computer assisted data analysis was carried out using a statistical analysis program. Analysis of significance ($p < 0.05$) involved paired and unpaired Student's two-tailed *t*-test. Correlation index (*r*) has been evaluated using a correlation coefficient matrix.

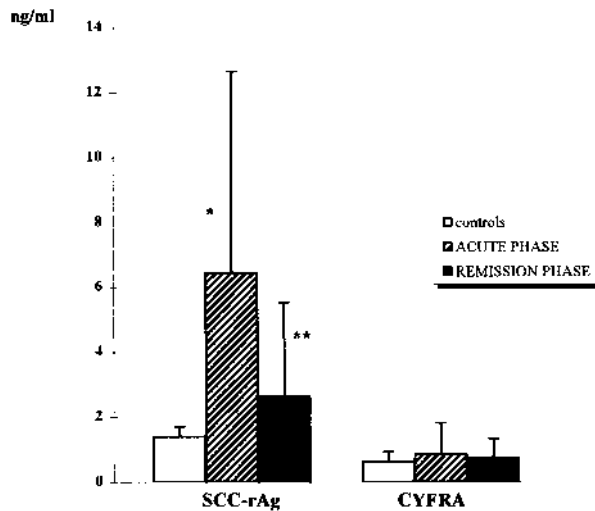


Fig. 1. Serum levels of squamous cell carcinoma related antigen (SCCr-Ag) and soluble cytokeratin 19 fragment (CYFRA) in psoriatic patients. * $p < 0.0001$ vs. controls. ** $p < 0.002$ between patients with acute and remission phase.

RESULTS

Our results clearly demonstrated high serum levels of SCCr-Ag in acute phase psoriatic patients with respect to controls (Fig. 1). In the same group of patients a statistically significant increase in IL-2, sIL-2R, sCD4, sCD8, sICAM-1 and β 2-microglobulin was observed (Table I). Furthermore, a positive correlation of SCCr-Ag was found with TBSA, PASI score, sICAM-1 and β 2-microglobulin in the acute phase of the disease (Fig. 2 and 3).

CYFRA did not show any modification compared with controls either in the acute or in the remission phase (Fig. 1).

In the patient group observed after remission we detected a significant reduction in SCCr-Ag levels (Fig. 1), TBSA and PASI score and sICAM-1 and β 2-microglobulin. However, none of these values returned to normal (Table I). Instead an increase in sCD8 and a trend toward a reduction in IL-2 was observed, while no significant modification of the other parameters tested was detected after the remission.

DISCUSSION

SCCr-Ag is a glycoprotein with a molecular weight of approximately 48,000 daltons. It is a subfraction of TA-4, a tumour

marker extracted by Kato & Torigoe in 1977 from squamous cell carcinomas of the uterine cervix (14). It has been documented that this antigen, present in the cytosol, is released in the bloodstream and may rise in patients suffering from squamous cell carcinoma especially when internal metastasis are present (17).

Our data clearly show a relationship between SCCr-Ag levels and the cutaneous involvement of psoriasis, as demonstrated by its positive correlation with TBSA and PASI score.

It is noteworthy that the CYFRA antigen, a marker of cytokeratin, is not increased in such patients. This apparent contradiction may be explained considering that in psoriasis there is an overall hyperproliferation of keratin 6 and 16 (18), rather than keratin 19, which is detected by anti-CYFRA monoclonal antibody.

The role of the immune system in the pathogenesis of psoriasis, has already been documented by several studies (1–11), and our previous reports demonstrated that the number of ICAM-1+ circulating lymphocytes and the levels of β 2-microglobulin present in the acute phase, correlated with the extension of the disease, underlining the relevance of such parameters in monitoring the disease activity (12, 13). Our present findings suggest a similar behaviour for SCCr-Ag in the acute phase; in fact it correlates with both immunological and inflammatory markers of disease activity such as sICAM-1 and β 2-microglobulin.

Soluble ICAM-1, the soluble form of the adhesion molecule ICAM-1, is released in the bloodstream after activation by cytokines and its rate is considered to be related to the inflammatory process in psoriasis (19). Similarly, the high levels of β 2-microglobulin, the invariant chain of MHC-I molecules, may reflect the rate of activation and proliferation of cutaneous cells (i.e. keratinocytes, Langerhans' cells, etc.). In this context we can hypothesize that the expression of SCCr-Ag, present in epidermal cells, and in turn its release in the bloodstream, may be induced by cytokines present in the microenvironment of psoriatic lesion. In the remission phase of psoriasis a reduction of SCCr-Ag levels with a parallel lowering of inflammatory parameters such as sICAM-1 and β 2-microglobulin is observed, further suggesting a common behaviour for such markers.

The presence of levels of sICAM-1 and β 2-microglobulin above normal mean values in the remission phase, reflects the persistence of residual activation of the skin inflammation and may be related to inadequate inhibition of up-regulated inflammatory cytokine production by local therapy alone; in this

Table I. Modification of % of total body surface area (TBSA), psoriasis area severity index (PASI) and immunological parameters in psoriatic patients

	Controls (n=20)	Acute phase (n=24)	Remission (n=24)	p-values for controls	p-values between patients in acute and remission phases
TBSA%		41.3 \pm 18.3	11.6 \pm 20.3		0.000
PASI		8.8 \pm 2.8	2.03 \pm 3.3		0.000
IL-2 (U/ml)	0.47 \pm 0.35	0.91 \pm 0.92	0.39 \pm 0.21	<0.05	
sIL-2R (U/ml)	627 \pm 174	906 \pm 569	1,235 \pm 936	0.044	
sCD4 (U/ml)	29 \pm 10	69.4 \pm 23.7	71.4 \pm 39.8	0.000	
sCD8 (U/ml)	276 \pm 69	371.6 \pm 145.6	450.9 \pm 133.7	0.001	0.0086
sICAM-1 (ng/ml)	215 \pm 92	508.5 \pm 154	363.6 \pm 86.5	0.000	0.03
β 2-microglobulin (ng/ml)	1.3 \pm 0.3	2.47 \pm 1.3	1.86 \pm 0.55	0.000	0.03

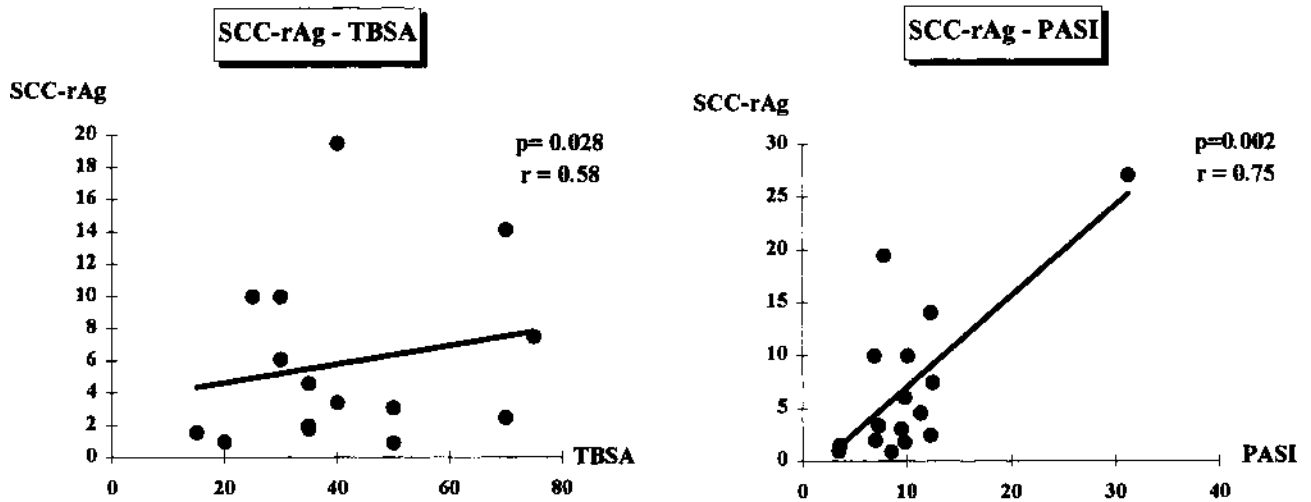


Fig. 2. Correlation of serum levels of squamous cell carcinoma related antigen (SCCr-Ag) between total body surface area (TBSA) and psoriasis area severity index (PASI) in patients in acute phase.

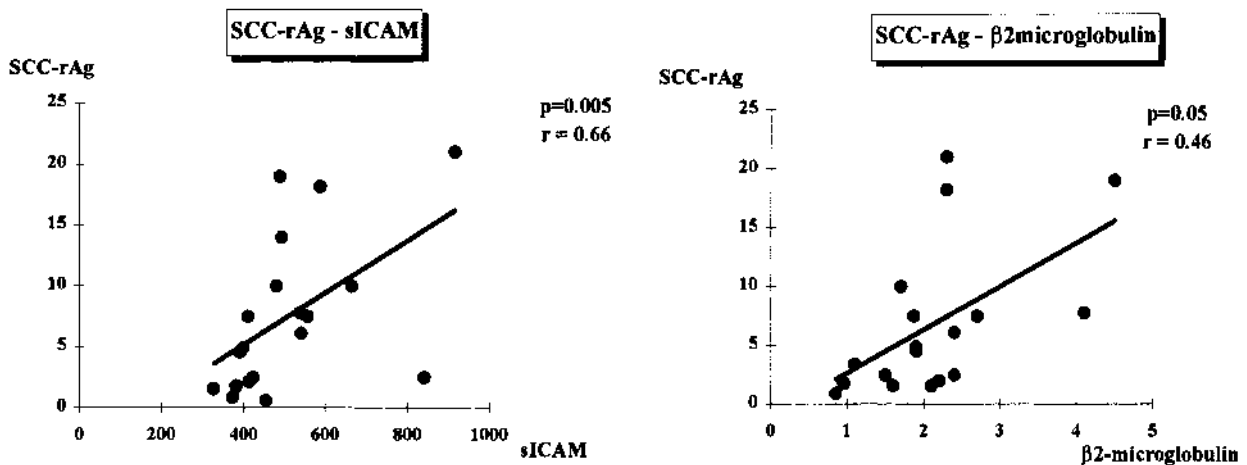


Fig. 3. Correlation of serum levels of squamous cell carcinoma related antigen (SCCr-Ag) between sICAM and β 2microglobulin in patients in acute phase.

respect it has been demonstrated that in psoriatic patients treated with systemic therapy a residual cytokine production is also present (20). Hence the detection of high amounts of SCCr-Ag in a patient affected by psoriasis does not necessarily imply the presence of a squamous cell carcinoma, but it should be considered as a sign of psoriatic disease activity. Thus, considering our results as a whole, we can suggest that SCCr-Ag may be part of the inflammatory process and may be considered as a marker of epidermal cell activity.

To our knowledge this is the first publication of a study of SCCr-Ag behaviour in patients affected by psoriasis which considers its relationship to other's immunological and inflammatory index of disease.

REFERENCES

- Jablonska S., Glinski W. Overview of immunology. In: Roenigk HH Jr, Maibach HI, eds. Psoriasis. New York: Marcel Dekker Inc., 1991: 261–283.
- Phillips TJ, Dover JS. Recent advances in dermatology. *N Engl J Med* 1992; 326: 167–176.
- Baadsgaard O, Fisher G, Voorhees JJ, Cooper KD. The role of immune system in the pathogenesis of psoriasis. *J Invest Dermatol* 1990; 95: 32S–34S.
- Krueger JG, Krane JF, Carter DM, Gottlieb AB. Role of growth factors, cytokines and their receptors in the pathogenesis of psoriasis. *J Invest Dermatol* 1990; 94 Suppl. 6: 135S–140S.
- Kupper TS. Role of epidermal cytokines. In: Oppenheim JJ, Shevach EM, eds. Immunophysiology. Oxford: Oxford University Press, 1990: 285–305.
- Jones JL, Berth-Jones J, Fletcher A, Hutchinson PE. Assessment of epidermal dendritic cell markers and T-lymphocytes in psoriasis. *J Pathol* 1994; 174: 77–82.
- Castells-Rodellas A, Castell JV, Ramirez-Bosca A, Nicolas JF, Valcuende-Cavero F, Thivolet J. Interleukin-6 in normal skin and psoriasis. *Acta Derm Venereol (Stockh)* 1992; 72: 165–168.
- Scheynius A, Fransson J, Johansson C, Hammar H, Baker B, Fry L, Valdimarsson H. Expression of interferon-gamma receptors in normals and in psoriatic skin. *J Invest Dermatol* 1992; 98: 255–258.
- Vollmer S, Menssen A, Trommler P, Schendel D, Prina JC. T lymphocytes derived from skin lesions of patients with psoriasis

- vulgaris express a novel cytokine pattern that is distinct from that of T helper type 1 and type 2 cells. *Eur J Immunol* 1994; 24: 2377–2382.
10. Gomi T, Shiohara T, Munakata T, Imanishi K, Nagashima M. Interleukin 1-alfa, tumor necrosis factor alfa, and interferon gamma in psoriasis. *Arch Dermatol* 1991; 127: 827–830.
 11. King LE, Gates RE, Stoscheck CM, Fava RA, Nanney LB. Role of epidermal growth factor in psoriasis. In: Roenigk HH, Maibach HI, eds. *Psoriasis*. New York: Marcel Dekker Inc., 1991: 431–433.
 12. De Pità O, De Sanctis G, Bottari V, Ruffelli M, Simoni R, Frezzolini A, Benucci R, Fontana L. ICAM-1 expression on peripheral blood lymphocytes from psoriasis: differences between acute and remission phase. *Chron Derm* 1995; 5: 203–211.
 13. De Pità O, Ruffelli M, Cadoni S, Frezzolini A, Biava GF, Simoni R, Bottari V, De Sanctis G. Psoriasis: comparison of immunological markers in patients with acute and remission phase. *J Dermatol Sci* 1996; 13: 118–124.
 14. Kato H, Torigoe T. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. *Cancer* 1977; 40: 1621–1628.
 15. Tsukahara T, Otoyama K, Horiuchi Y. Significance of elevated squamous cell carcinoma (SCC)-related antigen and lactate dehydrogenase (LDH) levels in senile erythroderma following eczema. *J Dermatol* 1993; 20: 346–350.
 16. Hamanaka S, Ujihara M, Numa F, Kato H. Serum levels of squamous cell carcinoma antigen as a new indicator of disease activity in patients with psoriasis. *Arch Dermatol* 1997; 133: 393–395.
 17. Horiuchi Y, Tsukahara T, Otoyama K. Immunohistochemical study of elevated expression of squamous cell carcinoma (SCC)-related antigens in erythroderma epidermis. *J Dermatol* 1994; 21: 67–72.
 18. Kato H, Nagaya T, Torigoe T. Heterogeneity of a tumor antigen TA-4 of squamous cell carcinoma in relation to its appearance in the circulation. *Jpn J Cancer Res* 1984; 175: 433–435.
 19. Iizuka H, Ishida-Yamamoto A, Honda H. Epidermal remodelling in psoriasis. *Br J Dermatol* 1996; 135: 433–438.
 20. Schopf RE, Naumann S, Rehder M, Morsches B. Soluble intercellular adhesion molecule-1 levels in patients with psoriasis. *Br J Dermatol* 1993; 128: 34–37.
 21. Shiohara T, Imanishi K, Sagawa Y, Nagashima M. Differential effects of cyclosporin and etretinate on serum cytokines levels in patients with psoriasis. *J Am Acad Dermatol* 1992; 27: 568–574.