OCCURRENCE OF IMMUNOGLOBULINS AND COMPLEMENT IN THE SKIN OF PATIENTS UNDERGOING TOPICAL TREATMENT OF MYCOSIS FUNGOIDES

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Abstract: Deposits of immunoglobulins (IgG, IgA and IgM) and complement were occasionally found in lesional skin of mycosis fungoides patients. However, after complete remission of the skin lesions, deposits of immunoglobulins and complement were found, corresponding to previous infiltrates or tumours, in about half of the patients. These deposits appeared as globular bodies in the upper part of the dermis closely connected with the basement membrane.

Key words: Mycosis fungoides; Immunoglobulins and Complement

Mycosis fungoides (MF) is a malignant T-cell lymphoma (2, 13) consistently localized in the skin before internal dissemination occurs. The etiology of MF is unknown, although some authors have suggested that an immune imbalance caused by persistent antigenic stimulation may lead to an autoimmune reaction and in some cases to the development of MF (11).

Lai A Fat & Cormane (7) demonstrated deposits of immunoglobulins and complement in lesional skin of MF patients. Such deposition coincided with the infiltrative stage, and was not found in the pre-mycotic stage, while a small number were discovered in the tumour stage.

This report deals with the detection of immunoglobulin and complement deposits in apparently healed skin lesions following treatment of MF patients.

MATERIALS AND METHODS

Sixteen MF patients were studied, all having a clinical course and findings typical of MF (Table I). The diagnosis was histologically verified in 14 cases and was fairly compatible with MF in the remaining 2 cases (nos. 1 and 4). Eleven of the patients were classified as being in the plaque stage, 4 in the tumour stage and one patient (no. 6) was diagnosed as a case of Sézary syndrome. Thirteen of the patients had previously received treatment for MF including topical corticosteroids (13 cases), superficial X-ray (4 cases, but not on the actual biopsy area in this study) and chemotherapy (1 case, no. 5). The actual treatment (Table I) was whole-body topical mechlorethamine (HN3) for 10 patients. Complete resolution of all skin lesions occurred in 9 of them, while the skin in one patient (no. 6) was almost normalized. Three patients achieved complete remission after treatment with the psoralen 8-MOP and longwave ultraviolet light (PUVA) (10).

Biopsy specimens from apparently normal and lesional skin (plaques and tumours) were obtained from 10 MF patients before treatment, and, after remission, from normal skin and from skin where a previous lesion had been present but which appeared normal at the time the biopsy was taken—except for pigment changes (hypo- and hyperpigmentation) in 13 cases. Biopsies were taken from exactly the same spot before and after treatment in 7 cases (nos. 1, 4, 6, 8, 9, 12 and 15).

Antisera and fluorochrome conjugates. Antibodies against human IgG, IgA, IgM, F(ab')2' and the complement factor C3 were produced in rabbits, correctly absorbed and thereafter conjugated with fluorescein-isothiocyanate (FITC) as described in detail by Husby et al. (1973). Normal rabbit IgG was also labelled with FITC and used as control conjugate.

 Immunofluorescence microscopy. Skin tissue specimens obtained at biopsy were embedded in OCT compound (Arnes Company, Indiana, USA) and immediately snap-frozen in dry ice-acetone. The sections were treated for 30 min in a moist chamber with the various FITC-conjugated antisera, washed twice for 15 min in phosphate-buffered saline, pH 7.4 (PBS), mounted in a 1:1 mixture of glycerol PBS (6). The stained sections were thereafter examined in a Leitz Orthoplan microscope with UV light source and filter combinations as described elsewhere (6). Micrographs were taken with an Orthomate camera.

Quantitation of serum immunoglobulins. Radial immunodiffusion (8) was employed for the determination of serum immunoglobulin (IgG, IgA, IgM) levels.

RESULTS

The results are presented in Table I. Before treatment with mechlorethamine or PUVA, deposits of
immunoglobulins were demonstrated in lesional skin in 2 out of 10 patients. The immunofluorescence staining was most intense in the Sézary patient (no. 6) and was much less pronounced in one MF patient (no. 4). Complement was found in only one patient (no. 16). The deposits of immunoglobulins and complement were seen as globular bodies in the upper part of the dermis in the Sézary patient and as granular deposits in the dermis closely apposed to the basement membrane in the MF patients. After healing of the cutaneous lesions, deposits of IgG and IgM and to a lesser extent IgA were detected in the skin of 7 out of 13 patients. Complement was found in the skin of 4 patients. The deposits of immunoglobulins and complement appeared as globular bodies of varying size located in the upper

Table I. Deposits of immunoglobulins and complement in lesional skin before treatment and in apparently normal skin on the same spot as a previous lesion after clearance

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Treatment</th>
<th>Stage before treatment</th>
<th>Clinical result</th>
<th>Before treatment</th>
<th>After treatment</th>
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<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
<td></td>
<td>IgG</td>
<td>IgA</td>
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<td>2</td>
<td>+</td>
<td>III</td>
<td>CR</td>
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<td>3</td>
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<td>4</td>
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<tr>
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<td>III</td>
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<tr>
<td>6</td>
<td>+</td>
<td>Sézary syndr.</td>
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<td>7</td>
<td>+</td>
<td>II</td>
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<td>8</td>
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<td>16</td>
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Fig. 1. Frozen section from an apparently healed skin lesion in a patient with mycosis fungoides stained with fluoresceinated anti-F(ab')₂ showing numerous globular bodies containing immunoglobulins (×200).
part of the dermis, closely connected with the base­
ment membrane (Fig. 1). To check the specificity
of immunofluorescence, it was shown that no simi­
lar staining was achieved with fluoresceinated nor­
mal rabbit IgG. In addition, specific immunofluores­
cence was completely abolished by pre-incubation
of the various fluoresceinated antisera with the rele­
ant antigens (IgG, IgA, IgM and C3). No immu­
noglobulins or complement were found in unaffect­
ed skin, either before or after treatment.
Normal immunoglobulin levels (IgG, IgA and
IgM) were found in the serum of all 16 patients
before and after clearance of the skin lesions.

DISCUSSION
This study showed that immunoglobulins and/or
complement were occasionally present in biopsy
specimens from lesional skin of MF patients, ob­tained before treatment. However, after healing of
the skin lesions, considerable amounts of immuno­
globulins and complement were found in apparently
healed skin, corresponding to the previous infiltra­
tes or tumours in many of the patients studied. The
findings suggest that deposition of immunoglobulins
and complement seems to take place during suc­
cessful skin treatment of MF.

Our findings differ to a certain degree from those
of Lai A Fat & Cormane (7), who demonstrated
deposits of immunoglobulins and complement in lesional skin before treatment in most of their MF
patients in the infiltrative stage. These authors
found immunoglobulins and complement located in
the blood vessel wall and scattered in the dermis.

In contrast to the findings in the MF patients, the
Sézary patient included in this study showed depo­
sition of immunoglobulins before treatment but not
after partial remission of the skin lesions. This find­
ing was unexpected, since it is impossible to dis­
criminate between these diseases histologically,
and since the same percentages of B- and T-
lymphocytes from erythrodermic skin of Sézary pa­
tients and from plaques of MF patients have been
found (1).

The mechanism of the deposition of immuno­
globulins and complement in healed skin at sites of
previous MF lesions is not clear. One possible an­
swer may be that such deposition is a result of the
treatment itself. The successful local treatment of
MF resulting in an effective depletion of lymphocy­
tes, mainly T-cells which have been shown to be
present in the skin lesions (1), may lead to a change
in the immunologic balance. Thus the T-cell deple­
tion may include loss of regulatory (suppressor)
lymphocytes and thereby disturb the ability of the
antibody producing cells (B-cells) to discriminate
between “self” and “not-self”, or simply make the
B-cells more active in antibody production. Anti­
gens from decomposed cells exposed during treat­
ment may then act as immunogens in vivo, result­
ing in the production and deposition of comple­
ment-fixing antibodies to such antigens. The globu­
lar bodies found in the upper part of the dermis
resemble the so-called ‘elastic globes’ which Hashi­
moto (4) revealed by electron microscopy were
derived from degeneration of basal epithelial cells.

It is interesting that we have seen internal dissemi­
nation of the disease in many patients studied by
the Scandinavian Mycosis Fungoides Study Group
a few weeks to months after complete healing of all
cutaneous lesions (3, 9). It therefore seems that a
certain protective mechanism connected with the
process in the skin may be abolished during suc­
cessful treatment of skin lesions. It is tempting to
assume that this factor is related to T-lymphocytes.
The skin lesions in MF may thus represent an im­
munologic surveillance system—possibly made up of
T-cells—which prevents internal/systemic dis­
semination of the disease. A similar protective ef­
effect of T-cells has been suggested for other malign­
ant tumors (6). As soon as these lesions heal as a
result of local treatment, such dissemination will
tend to occur. This would also explain the protract­
ed course of the disease which is observed in many
patients where clearance of skin lesions does not
occur.

REFERENCES
1. Burg, G. & Braun-Falco. O.: Classification and differ­
eniation of cutaneous lymphomas. Enzyme-cyto­
chemical and immunocytochemical studies. Br J Derma­
2. Edelson, R. L., Lutzner, M. A., Kirkpatrick, Ch. J.,
Shewach, E. M. & Green, J.: Morphologic and func­
tional properties of the atypical T-lymphocytes of Sé­
dissemination of mycosis fungoides despite successful
local therapy. Acta Dermatovener (Stockholm) 58: 88,
1978.
4. Hashimoto, K.: Apoptosis in lichen planus and seve­
rnal other dermatoses. Acta Dermatovener (Stock­
Acta Dermatovener (Stockholm) 59


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