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Immunoglobulin and Complement Deposits in the Skin and Circulating Immune Complexes in Scabies

O. P. Salo, T. Reunala,[1] K. Kalimo[2] and T. Rantanen[1]

Departments of Dermatology, University Central Hospitals of Helsinki, [1]Tampere and [2]Turku, Finland

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Abstract. Sixteen patients with papulovesicular, 6 with nodular and one with a Norwegian scabies were studied. Direct immunofluorescence (IF) examination revealed C_3 deposits in the skin lesions of 13 of the 18 patients. Among them were all 6 cases with nodular scabies. C_3 was found mostly in dermal vessel walls and 3 of the patients also showed IgM and 2 IgA deposits at the same site. No circulating immune complexes were found, with a solid-phase C_{1q} radioimmunoassay (RIA), but HSV- and RSV-RIA methods detected IgM antibodies of rheumatoid factor type in 5 of the 15 sera examined. These results suggest that local complement activation and perhaps also immune complex deposition may be important in the pathogenesis of the papular and nodular skin lesions of human scabies.

Key words: Scabies; Complement deposits; Immune complexes

The clinical symptoms of scabies only develop after a certain period of incubation. Mellanby (8) showed that after a primary scabietic inoculation it takes about one month before the itching and papulovesicles appear, but in a reinfection the symptoms develop within 24 hours. The development of immediate skin test reactivity and the occurrence of circulating IgE antibodies to scabies mite indicate that IgE-mediated hypersensitivity plays a role in the manifestation of human scabies (3, 10). Recent reports of immunoglobulin and complement deposits in the skin lesions suggest that mechanisms other than IgE-mediated are also involved (4, 5).

In a preliminary immunofluorescence (IF) study (11) we found deposits of the third component of complement (C_3) in dermal vessel walls of scabietic lesions. In this study we report IF findings in skin lesions and the occurrence of circulating immune complexes and IgM antibodies of rheumatoid factor (RF) type in papulovesicular, nodular and Norwegian scabies.

PATIENTS AND METHODS

Twenty-three patients, 18 males and 5 females, with scabies were examined. The diagnosis was confirmed by demonstrating a live mite in every patient. The mean age of the patients was 30 years and the mean duration of the clinical symptoms 3 months. Sixteen patients had a papulovesicular scabies with varying degrees of small vesicles and papules and 6 patients had a nodular form of scabies with many persistent nodules located mostly on genitals, groins and axillae. One patient had been treated for 2 months with peroral and topical steroids and he had developed crusted lesions with many mites i.e. the clinical picture of Norwegian scabies.

Skin biopsies were taken from 18 patients, from 16 of them before any treatment with a scabicide. The specimens were divided for routine histology (haematoxylin and eosin) and IF-examinations. In the latter, the specimens were examined for IgG, IgM, IgA and C_3 with commercial FIC-conjugated antisera (Behringwerke, Marburg, F.R.G.) using ordinary methods for direct IF. At least three tissue sections per conjugate were examined and the degree of fluorescence was graded as strong (+++), moderate (++), weak (+) and no (−) fluorescence.

Serum specimens from 15 patients were taken before any treatment and were stored at −50°C. For the presence of anti-immunoglobulins, the RFs were demonstrated by two methods. In these, herpes simplex virus (HSV) or respiratory syncytial virus (RSV) were used as antigens to which human IgG was bound. This antigen–antibody complex was fixed to a solid phase as reported earlier (6). The RF in the serum samples attached to these complexes was detected by radiolabelled antihuman IgM. In the third method, C_{1q} was attached to a solid phase and complexes bound from the serum were demonstrated by radiolabelled antihuman IgG (1).

Serum IgG, IgM, IgA and complement (C_3, C_4) levels were determined with a laser nephelometer method (Behring Institute, Marburg, F.R.G.). Normal limits for IgG were 8–18 g/l, for IgM 0.6–2.5 g/l, for IgA 0.9–4.5 g/l for C_3 0.45–1.1 g/l and for C_4 0.2–0.5 g/l.

Table I. *Immunofluorescence (IF) and histopathological findings in 18 patients with various clinical forms of scabies*

Patient and sex	Age (yrs)	Duration of disease (months)	IF in dermal vessels			Degree of perivascular cellular infiltrates
			C_3	IgM	IgA	
Papulovesicular scabies						
S.M. ♀	13	1.5	++[a]	–	–	+++
P.R. ♂	25	2.5	+	–	–	+
J.V. ♂	23	2	++	–	–	+
s.s. ♂	26	6	++[b]	–	–	+
V.S. ♂	26	3	++	–	–	+
U.N. ♀	15	1	+++	+	–	+
S.V. ♂	30	3	–	–	–	–
A.O. ♀	60	6	–	–	–	+
P.M. ♀	24	5	–	–	–	–
L.A. ♀	44	4	–[b]	–	–	+
J.E. ♂	23	1	–	–	–	+
Nodular scabies						
R.G. ♂	40	3	+++	+	+	++
E.K. ♂	53	2	+++	–	–	++
T.L. ♂	34	4	+	+	+	+++
E.R. ♂	26	2	+	–	–	++
H.K. ♂	26	0.5	+++	–	–	++
O.T ♂	44	3.5	++[b]	–	–	++
Norwegian scabies						
H.L. ♂	29	6	–	–	–	++

[a] Degree of fluorescence.
[b] Present at the basement membrane zone between epidermis and dermis.

RESULTS

IF examinations demonstrated C_3 deposits in 13 (72%) patients (Table 1). Twelve patients had C_3 in the dermal vessel walls and 3 had C_3 in the basement membrane zone. C_3 was found mostly in the deeper dermal vessels, but 3 patients had C_3 deposits also in the vessels of the papillary dermis. All six specimens from scabietic nodules had C_3 and in three of them the intensity of the fluorescence was strong (+++). In two nodular and one papulovesicular case IgM occurred at the same sites as C_3 and IgA was also found in two of these specimens (Table1).

Dense dermal cellular infiltrates were typical for the specimens with C_3 deposits but were also seen in three specimens with noC_3 deposits (Table 1). The infiltrates were mainly perivascular and consisted of lymphocytes and histiocytes with varying amounts of eosinophils but only a few polymorphonuclear leukocytes.

No circulating IgG complexes were detected with the C_{1q}-RIA. IgM antibodies of the RF type were detected in five out of 15 serum samples examined by HSV- and RSV-RIA (Table II) and both tests were positive in 3 patients. All positive samples were from patients with papulovesicular scabies.

The mean level for serum IgG was 15.1±5.0 g/l, fro IgM 1.44±0.6 g/l, for IgA 3.26±1.7, for C_3 0.66±0.16 and for C_4 0.24±0.07 g/l. Two patients had elevated levels of both IgG and IgA. One patient had a high IgA level and low levels of C_3 and

Table II. *Circulating immune complexes and RF in 15 patients with scabies, measured with various solid-phase radioimmunoassays*

Patients	HSV-RIA[a]	RSV-RIA[a]	C_{1q}-RIA[b]
Papulovesicular scabies (n=11)	4[c]	4	0
Nodular scabies (n=4)	0	0	0

[a] IgM anti-immunoglobulins (RF).
[b] IgG complexes.
[c] Number positive.

C_4. However, no correlation was found between serum Ig and complement levels, RFs, or skin IF findings.

DISCUSSION

The present study showed that C_3 deposits are common in scabietic skin lesions and particularly in dermal vessel walls of the nodular lesions. A recent study of 4 patients with scabies (5) showed C_3 deposits in the vessels of the papillary dermis, whereas in this study C_3 was found mainly in the deeper dermal vessels. The discrepancy seems to be due to the different types of lesions biopsied. Hoefling & Schroeter (5) biopsied the suspected burrow areas, whereas in this study papules or nodules were selected. In addition to dermal vessels, C_3 occurred at the basement membrane zone between epidermis and dermis in 3 of the present patients, which is a deposition pattern also reported earlier (4, 5).

About 7% of the patients with scabies develop nodular lesions which are known to persist for a long time after the treatment with a scabicide (7). This may be due to the persistence of antigenic material in these nodules. In this study all 6 patients with nodular scabies had C_3 deposits in dermal vessels. In one of these patients the biopsy was positive 2 months after the treatment, suggesting that factors activating complement were still present. Seven of the 11 patients with papulovesicular scabies had C_3 deposits, showing that complement activation plays a role also in this form of scabies. The patient with a Norwegian scabies had no C_3 although the skin specimen showed marked inflammatory changes. Norwegian scabies often occur in immunodeficient or immunosuppressed patients. Our otherwise healthy patient had been treated for 2 months with peroral steroids and the negative skin IF may have resulted from the altered humoral response due to the steroid treatment. Interestingly, this patient had a very high level of serum total IgE (10).

IgM, IgA and C_3 deposits are frequently found in dermal vasculitis where they probably represent immune complex deposition (2). In this study IgM and IgA deposits were found at the same sites as C_3. Therefore, it seems that immune complex deposition occurs also in scabies and plays a role in the pathogenesis of the scabietic lesions. We tried to detect circulating immune complexes but no IgG complexes were found with the C_{1q}-RIA. This is in agreement with a previous study (9) in which such complexes were reported only in a treated (but not in an untreated) group of patients. In the present study 5 patients had circulating IgM antibodies of RF type but there was no correlation to skin IF, or to serum Ig and complement levels. The significance of these autoantibodies remains open. However, such antibodies have been found with the present methos in diseases with frequent immune aberrations, i.e. in lupus erythematodes and dermatitis herpetiformis, but not in normal controls, suggesting that in scabies the production could result from humoral response to mite antigen–antibody complex.

In addition to immune complex deposition, antigen–antibody complexes could also from *in situ* and activate the complement system with the resultant generation of potent mediators of inflammation. The persistence of antigenic material of the mite in the skin could in turn result in a continuous local inflammatory reaction causing the visible papules and nodules and the dense cellular infiltrates in these lesions. The histology of nodular scabies can even simulate skin lymphomas (12) and, consequently, the IF examination revealing C_3 deposits in dermal vessels could help in differentiating persistent scabietic nodules from malignant lesions.

It is evident from earlier studies that immediate hypersensitivity plays a role in the manifestations of human scabies. The results of the present study show that mechanisms activating complement and perhaps also deposition of immune complexes are also involved, particularly in nodular scabies. Cell-mediated immunity may also be important in the host response to scabies mite, but this remains to be verified in further studies.

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Normal Sweating and Tear Production in Congential Ichthyosiform Erythroderma with Deafness and Keratitis

J. J. E. van Everdingen, F. H. J. Rampen and W. W. van der Schaar

Academisch Medisch Centrum, Department of Dermatology, Meibergdreef, 1105 AZ Amsterdam, The Netherlands

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Abstract. A 24-year-old female patient with congenital ichthyosiform erythroderma, deafness and vascularizing keratitis yet also exhibiting normal sweating and tear production when tested is reported. This unique finding indicates that a certain subgroup of patients with this generalized ectodermal disturbance may benefit from treatment with the aromatic retinoids.

Key words: Ichthyosiform erythroderma; Sweating; Tear production; Aromatic retinoids

The group of ichthyosiform dermatoses comprises the normokinetic ichthyoses (ichthyosis vulgaris and X-linked ichthyosis), the hyperkinetic forms (epidermolytic hyperkeratosis and the lamellar ichthyoses), and a complex category of congenital ichthyosiform syndromes associated with other developmental defects (1). The latter group harbours a rare disorder of ichthyosiform erythroderma with deafness and vascularizing keratitis, which was probably first described by Burns in 1915 (2). A consistent finding in this syndrome is the dry skin, referred to as "anhidrosis", reported by several authors (2–7). Recently, however, we investigated sweat and tear production in a patient with this syndrome and discovered that they both appeared normal.

CASE REPORT

A 24-year-old woman was referred to our Department because of a generalized eruption of the skin which had been present since birth. She was the youngest of nine siblings. There was no family history of this disorder and no consanguinity. Soon after birth the skin became thickened, scaly and reddish. Almost complete deafness was noted at the age of 4. From the age of 11 she had been photophobic and the right eye subsequently displayed marked visual loss. Dentition was incomplete and the teeth were malformed and showed carious signs at an early age. Genital development was uncomplicated and menarche occurred at the age of 16. Her psychosocial progress was considered satisfactory when compared with other deaf children.

On examination, her skin appeared universally ichthyotic with a red hue, especially on the face and limbs, and also showed some scaling. The palms and soles were hyperkeratotic. The scalp hair was rathers canty, eyebrows and eyelashes were sparse, and axillary and pubic hair were totally absent. The nails showed thickening and dystrophic changes.

Ophthalmological examination disclosed keratoconjunctivitis with extensive vascularization of the corneal epithelium with pannus formation of both eyes. Bullous dystrophia was seen in the lower segment of the right cornea but corneal ulcerations were not encountered. The visual acuity of the right eye was grossly diminished (1/6), whereas the left eye enjoyed normal vision. Tear production (Schirmer test) and composition, including IgA, were normal. Audiometric examination demonstrated profound perceptive (neurosensory) deafness in both ears.

Sweating on the forearm and the palm of the hand was investigated by the starch iodine test (Minor test). Sweating was normal on two occasions when compared with a control person. The more quantitative method as described by Thomson & Sutarman (8) was also performed. This test allows the recording of active palmar digital sweat glands. Numerous active sweat glands were encountered, indicating that our patient was not anhidrotic