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COEXISTENCE OF LUPUS ERYTHEMATOSUS AND SCLERODERMA IN LIGHT OF IMMUNOPATHOLOGICAL INVESTIGATIONS

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Abstract. The paper describes three cases of scleroderma (S) with coexistent lupus erythematosus—the discoid form (DLE) in one and the systemic form (SLE) in two patients. Scleroderma was diagnosed on clinical and histopathological evidence and typical additional findings (prolonged sensory chronaxy in the entire skin, radiological findings in the esophagus and bones). Demonstration by immunofluorescent method of in vivo-fixed immunoglobulins and complement in the epidermal–dermal junction was highly suggestive of coexisting LE. In discoid LE (DLE) the immunofluorescent staining was positive exclusively in the LE lesion, negative in the sclerodermatous skin. In SLE the results were positive in the LE lesions as well as in the sclerodermatous and the unchanged skin. Immunopathologic investigations may be important in clinically unclear cases of possibly coexisting collagen diseases.

Coexistence of different collagen diseases has been frequently described in the literature (2, 3, 10, 14, 16, 17, 18).

In typical cases, differentiation between them does not present major difficulties. However, in some cases the clinical pattern includes symptoms which may correspond to more than one of the different entities within this group, e.g., dermatomyositis (Dm) + scleroderma (S), or Dm + SLE + rheumatoid arthritis (R.A.).

Differentiation is sometimes difficult because laboratory findings are not always diagnostic. For instance, antinuclear antibodies, whose high titer is characteristic of SLE, may occur in scleroderma, rheumatoid arthritis, and dermatomyositis, as may also the LE factor (1, 15, 19, 20, 22, 23, 24, 26). On the other hand, electromyographic abnormalities and high levels of phosphokinase, aldolase, and transaminases may exist not only in Dm, but also in other collagen diseases with muscular involvement, e.g. in S and SLE (11).

In the present paper three cases of coexistence of LE and S are described. In the first case a discoid LE coexisted with typical scleroderma; in the second there were coexistent lesions of SLE and S; and in the third, the skin lesions were not diagnostic but with some features of incipient S and R.A. Our aim is to show the importance of immunopathological investigations in the diagnosis of LE and its differentiation from other collagen diseases.

MATERIAL

The material comprises three cases of coexistence of SLE and S. Ten cases of scleroderma and 88 cases of LE (55 of discoid LE and 33 of SLE) served as controls together with 85 cases of other diseases.

IMMUNOPATHOLOGICAL INVESTIGATIONS

Specimens were immediately frozen in liquid air and cut in a cryostat to a thickness of 3–4 μ at $-20°$C.

Washed in buffered physiological saline (pH 7.2) and air-dried, the unfixed sections were covered with unlabelled rabbit immune sera (IS) directed against human IgM, IgA (Behringwerke, Marburg a. d. Lahn) and β_1C (Central Laboratory of the Netherlands Red Cross Blood Transfusion Center, Amsterdam), and then with fluorescein isothiocyanate-labelled goat IS against rabbit globulins (Baltimore Biological Laboratories). IgG was detected by the direct method with fluorescein isothiocyanate-labelled IS against human fraction 7S* (pure IgG obtained by fractionation on a DEAE cellulose column was used for the immunization of rabbits).

The preparations were washed twice in phosphate-buffered saline, sealed in buffered glycerin, and observed in a fluorescence microscope (Fluorolume-American Optical Company).

The specificity of the immunofluorescence reaction was checked by blocking reactions; in the indirect method the preparations incubated with a suitable IS were then covered with unlabelled and labelled goat anti-rabbit glob-

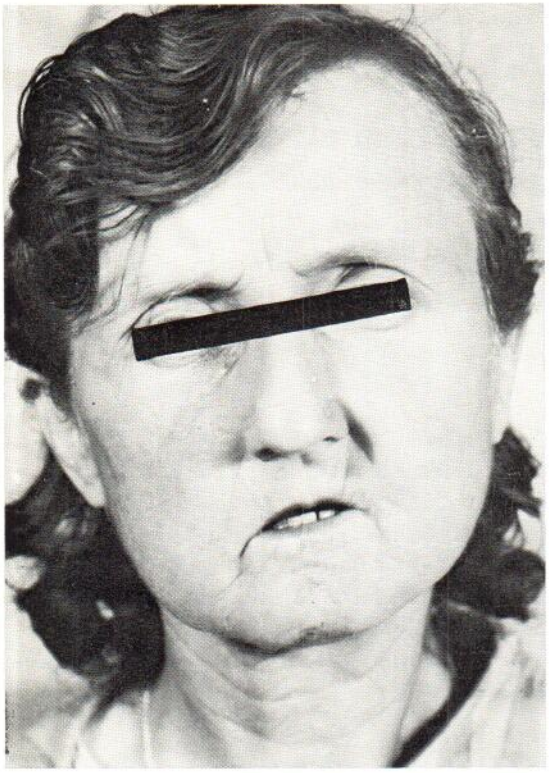

Fig. 1. Skin lesions on the face typical of scleroderma.

ulin sera in that order; in the direct method the sections were covered with unlabelled and labelled anti IgG sera in that order.

Antinuclear factors were detected by the indirect method of Weller & Coons (25), with rabbit epithelium and rat liver as substrates and the anti-IgG conjugate as above.

CASE REPORTS

Case 1

A woman aged 50 had had Raynaud's phenomenon since 15 years of age and indurations since the age of 40. For the last seven months before admission she had erythematous scarring lesions on the scalp and for several months erythematous lesions on the face. The skin lesions on the upper extremities and face are typical of scleroderma (Fig. 1) and there are typical discoid LE lesions in the face and scalp (Fig. 2).

Among the laboratory findings the following suggest scleroderma: sensory chronaxy was prolonged throughout the seemingly normal skin (11); capillaroscopy showed the deformed scleroderma-type of loops and the Raynaud-type giant loops; plethysmography showed organic changes in the vessels. X-rays of the oesophagus, lungs, and bones of the hands showed changes typical of scleroderma. Electromyography showed primary muscular changes.

Immunoelectrophoresis revealed markedly elevated IgG, IgM, and α2M globulin features. The proteinogram shows hypergammaglobulinemia. LE factor (−); antinuclear factor (ANF) by the immunofluorescence method (−).

Immunopathological investigations of lesions of the face and scalp revealed in vivo-fixed immunoglobulins and complement in the epidermal–dermal junction. Histology of the facial lesion was typical of LE.

Immunopathological investigation of sclerodermatous lesions did not reveal specific fluorescence.

Case 2

A woman aged 51 years had scleroderma and SLE. The disease began 12 years previously with Raynaud's phenomenon and gradually developing induration in the fingers and facial skin. She had erythematous hyperkeratotic lesions on the face, upper extremities and buttocks which developed some months ago (Fig. 3). The following laboratory findings suggested scleroderma: slight re-

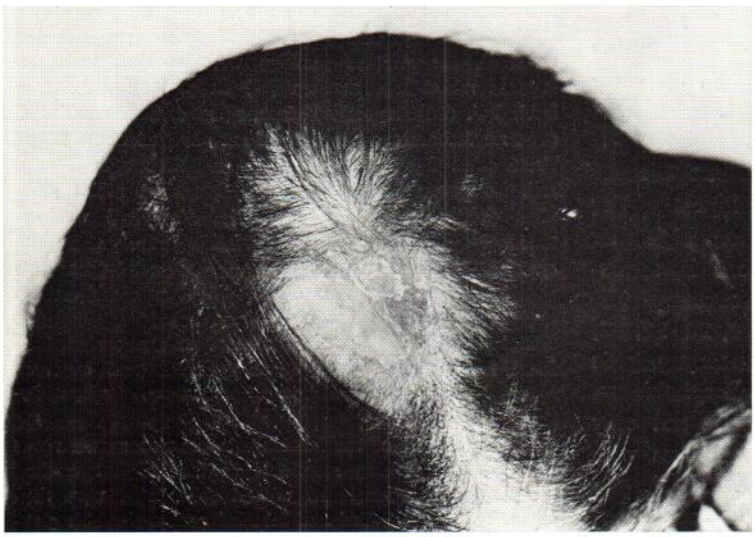

Fig. 2. Case 1. Discoid lupus erythematosus in the scalp.

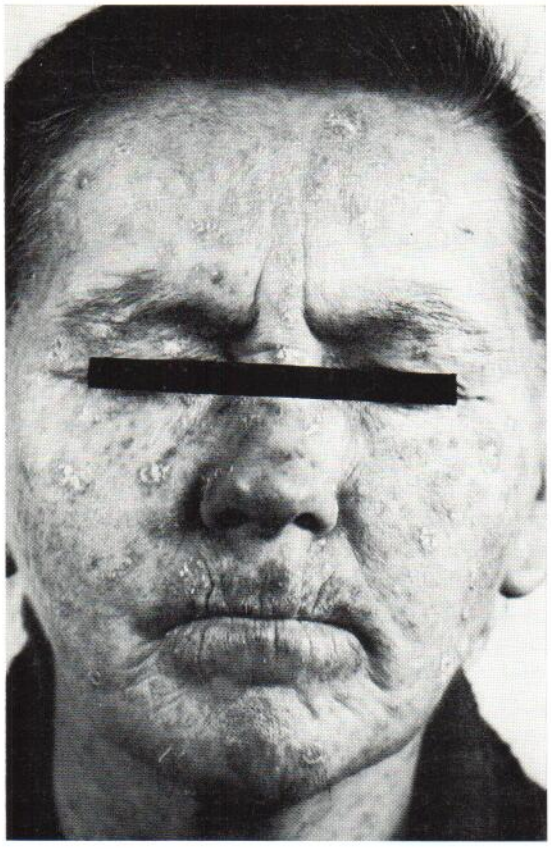

Fig. 3. Case 2. Hyperkeratotic erythematous lesions in the face typical of lupus erythematosus. Radial furrows around the mouth characteristic of incipient scleroderma.

sorption of the terminal phalanges in the hands and some dilatation of the oesophagus were shown by X-rays; sensory chronaxy was prolonged in the entire seemingly unchanged skin (11), capillaroscopy demonstrated the distorted capillaries typical of S together with some giant loops, which are characteristic of Raynaud's syndrome (11); plethysmography revealed functional changes in the arterioles of the fingers.

EMG (–). Transaminases elevated.

Laboratory findings suggesting SLE were: ANF titer 1 : 1280 (during treatment much lower 1 : 160, 1 : 40, 1 : 20), LE phenomenon negative; hypergammaglobulinaemia, and in immunoelectrophoresis, elevated IgG, slightly elevated IgM, α_2 ceruloplasmin and α_2 lipoprotein. Urinalysis: protein, leukocytes and erythrocytes. Waller-Rose test: 1 : 80 – 1 : 40.

The presence of in vivo-fixed immunoglobulins and complement in the dermal–epidermal junction of specimens from the hand dorsum, elbow, buttocks and face was highly suggestive of LE. The histology of these lesions was not diagnostic, neither did it exclude nor confirm the diagnosis of LE.

Case 3

A woman aged 39 years. The disease began seven years ago with arthralgia and Raynaud's phenomenon. Deformities of the fingers existed over the last four years (Fig. 4). The patient was treated six years for rheumatoid arthritis. Two years ago SLE was diagnosed in another hospital, chiefly on the evidence of the LE phenomenon. Owing to progressive indurations in the hands and face which commenced a year ago, she was referred to this Clinic with a tentative diagnosis of S for further investigations. The skin indurations in the hands suggested incipient S. The SLE lesions developed in the hands during further observation.

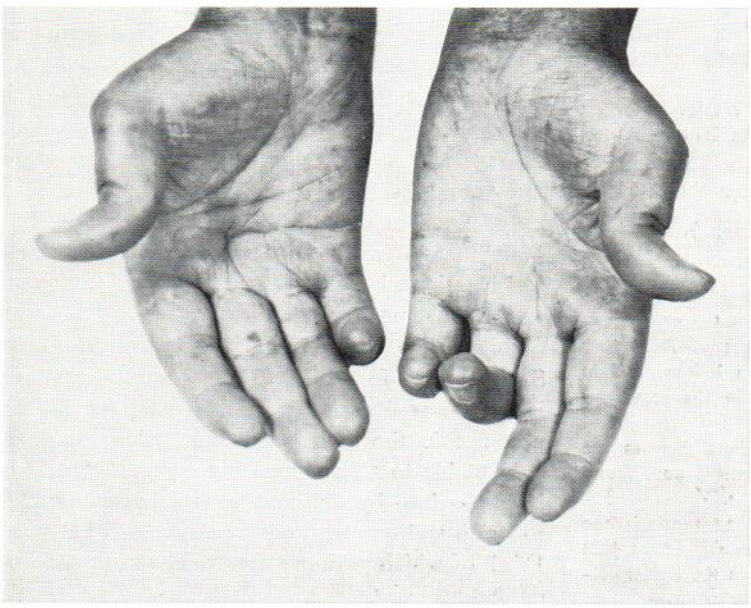

Fig. 4. Case 3. Deformities of the fingers consistent with rheumatoid arthritis.

Fig. 5. Indirect IF staining with an anti-complement immune serum. Specific fluorescence in the dermo–epidermal junction (specimen from uninvolved skin).

The following laboratory findings suggested S: there was radiological evidence of the resorption of the terminal phalanges in the hands and dilatation of the oesophagus; sensory chronaxy was prolonged in the healthy as well as the changed skin (11), capillaroscopy demonstrated the distorted capillaries typical of S and some giant loops characteristic of Raynaud's syndrome; functional changes in the digital arteries were revealed by plethysmography. SLE was suggested by leukopenia (3200 white cells), high sedimentation rate (up to 85/116), urinalysis (protein, hyaline casts, and occasional leukocytes), hypergammaglobulinemia (30%). In immunoelectrophoresis IgG, IgM and α_2 ceruloplasmin were elevated and β_1C was lowered. ANF 1 : 640. LE factor (−).

Immunopathological examination of the unchanged skin showed in vivo-fixed IgM and complement in the dermal–epidermal junction (Fig. 5).

It is emphasized that at times the Waaler–Rose test showed a high titer (160–1280), and the Latex RA test +++.

Immunopathological investigations in the remaining cases

In ten cases of scleroderma no in vivo-fixed immunoglobulins or complement were detected in the epidermal–dermal junction, whereas in all 55 cases of DLE they were present in this localization in skin lesions, and in 33 SLE cases they were present also in the seemingly unchanged skin.

Among the 85 control cases of various diseases the in vivo-fixed immunoglobulins or complement were found in two out of five cases of dermatomyositis.

In three out of five cases of pustular psoriasis the IF findings resembled those in pemphigoid, i.e. a thin line of specific fluorescence was present in the epidermal–dermal junction.

DISCUSSION

The discovery of in vivo-fixed immunoglobulins in the epidermal–dermal junction in LE, reported independently by Burnham et al. (4) and Cormane et al. (8, 9) was a breakthrough in the diagnosis of this disease.

Subsequent investigations have shown that the immunoglobulins are accompanied by in vivo-fixed complement (12, 13), which is of basic diagnostic significance because the complement is a regular component in this location, whereas the immunoglobulin composition may vary (7, 9, 13, 21).

In SLE the in vivo-fixed immunoglobulins and complement occur not only in the area of skin lesions but also in the unchanged skin (9), even in cases without cutaneous lesions. In DLE they are found exclusively in the area of the lesions.

The findings are characteristic of LE (9, 13) and, as has also been our experience (6, 7), provide a basis for diagnosing or excluding LE in clinically doubtful cases. The IF method has been used to demonstrate LE coexistent with pemphigus in the Senear-Usher syndrome (5), and enables LE to be diagnosed in atypical cases which show the symptoms of other collagen diseases. This was previously impossible because neither detection of the antinuclear factor by the immunofluorescence method nor the LE phenomenon are fully specific.

The immunoglobulins and complement occurring in the epidermal–dermal junction have never been a finding in our cases of scleroderma in which the disease was diagnosed on the evidence of clinical and histological features jointly with other abnormal results of laboratory examinations [X-rays and sensory chronaximetry in the seemingly normal skin (11)].

In the case of scleroderma with discoid LE, immunoglobulins and complement were present in LE lesions, but were absent in the sclerodermatous and the normal skin.

But in the two cases of coexistent SLE and S they were found in LE and sclerodermatous lesions as well as in the normal skin. That their presence in the sclerodermatous lesions was not attributable to scleroderma but to coexistent SLE is emphasized by the controls—ten cases of scleroderma and one with coexistent discoid LE (case 1), all of which gave negative results in the sclerodermatous lesions.

It is interesting that in the third case, immunoglobulins in the epidermal–dermal junction had IgM as the exclusive component and this case showed a very high titer of the rheumatoid factor.

The immunopathological method made it possible to diagnose SLE with reasonable certainty in the present cases of collagen diseases, which were clinically not clear.

However, it should be emphasized that this method should not be considered as decisive in the differential diagnosis between LE and dermatomyositis.

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