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DISCOID LUPUS ERYTHEMATOSUS AT THE SITE OF AN INTRADERMAL INJECTION OF KILLED *STAPHYLOCOCCUS AUREUS*

KATHERINE GRICE, DEBORAH DONIACH AND J. L. TURK

The Institute of Dermatology, St John's Hospital for Diseases of the Skin, London, and The Middlesex Hospital, London

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SUMMARY

A case of chronic discoid lupus erythematosus is described in which there were recurrent relapses following infections, and at the same time repeated 'flare ups' at the site of a delayed hypersensitivity reaction to *Staphylococcus aureus*. The appearance of the injection site changed from that of a typical 'tuberculin reaction' to a patch of discoid lypus erythematosus which was confirmed both histologically and by immunofluorescence.

INTRODUCTION

Lupus erythematosus (LE) is associated with multiple autoimmune phenomena, and in the skin lesions deposits of antigen–antibody complexes have been demonstrated by immunofluorescence (Burnham, Neblett & Fine, 1963; Cormane, 1964; Kalsbeek & Cormane, 1964; Tan & Kunkel, 1966; ten Have-Opbroek, 1966a, b). The factors which contribute to initiate these lesions appear to be multiple. It has been suggested that leakage of enzymes from connective tissue cells might be involved, and the effect of chloroquine or hydrocortisone on LE could then be explained by a stabilization effect on lyosomes, while ultraviolet light which exacerbates LE is known to disrupt lysosomes (Weissmann, 1964; Roburn, 1965). However, it has also been suggested that bacterial antigens, possibly from the normal flora, may be responsible for the systemic manifestations (Stevens, 1964) and for the skin lesions (Barber, 1941). Drugs, injections of tuberculin or horse serum, insect bites, burns, physical trauma, pregnancy and thymectomy have been described as precipitating or initiating the disease (Domz, McNamara & Holzapfel, 1959; Zingale *et al.*, 1963; Gold & Gowing, 1953; Mund, Simson & Rothfields, 1963; Alarcón-Segovia *et al.*, 1963; Rheumatism Review, 1966). We have observed a patient (Grice, 1966) with widespread chronic discoid LE who developed a recurrent patch of lupus erythematosus at the site of an intradermal injection of staphylococcus aureus.

Correspondence: Dr Katherine Grice, The Institute of Dermatology, St John's Hospital for Diseases of the Skin, London, W.C.2.

CASE REPORT

E.T., a woman aged 45 years, working as a nurse in a chest clinic first attended St John's Hospital in 1949 when she was diagnosed as having discoid lupus erythematosus. At that time she presented with a year's history of a rash affecting her face, neck and upper limbs. There was no history of drug taking and the histological appearance of the skin lesions was compatible with the clinical diagnosis. An X-ray of her sinuses showed bilateral mucosal thickening. The ESR was repeatedly normal. Seven years previously (1942) she developed thyrotoxicosis for which she eventually had a subtotal thyroidectomy. At the same time she was found to have

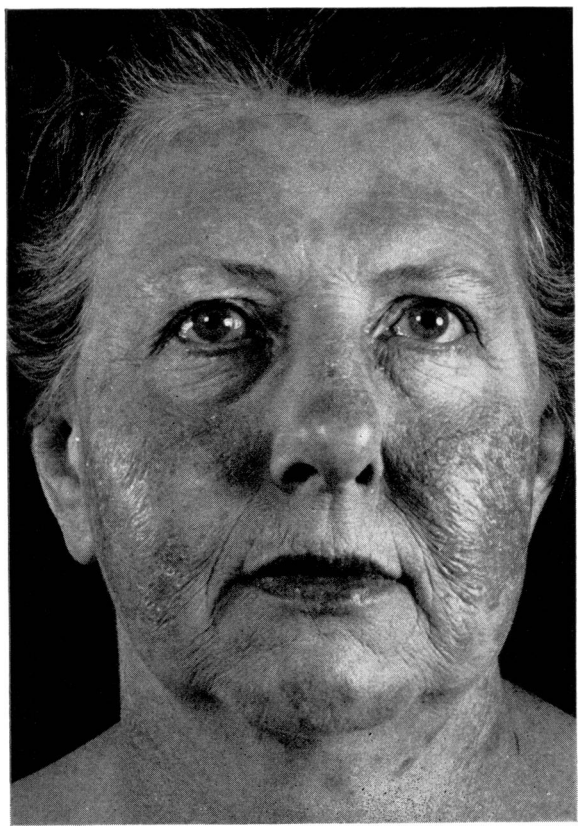

FIG. 1. Patient E.T. with discoid lupus erythematosus, showing scarring and erythema of the cheeks, nose and forehead.

bilateral tuberculous pulmonary apical infiltrations. Repeated examinations of her sputum failed to reveal the presence of *M. Tuberculosis*. The Mantoux test with old tuberculin 1:10,000 was negative in 1949, but was positive to 1:1000 in 1952. Her chest X-ray has not varied significantly since 1950 apart from some hardening and calcification of the apical lesion in the first years. She has occasional attacks of asthma which started in 1945. In 1947 she had pneumonia. At that time she was treated with sulphamezathine and penicillin for a few weeks. A course of penicillin was also given in 1946 at the time of the thyroidectomy. In 1955 she was given streptomycin 1 g twice per week and isoniazid 200 mg/day for 10 months. She has never been pregnant.

Since the onset of the LE in 1948, the rash has been persistent, although it nearly clears in winter, and relapses in summer. Her cheeks, bridge of the nose, and forehead have been most severely affected and there is marked scarring of the cheeks (Fig. 1). The light exposed areas of the neck, chest and hands have been affected by papular erythematous lesions. There has been swelling with erythema and telangiectasia over the proximal and middle phalanges.

In 1949, she had radiotherapy (90 kV) to her face, arms and hands. A total of 200 r in four divided doses at 2-weekly intervals was given to her face and 150 r in three doses to her arms and hands. She was given chloroquine sulphate 600 mg daily for 2½ years in 1955. This controlled the skin lesions but she developed punctate deposits in both corneae and was then given hydroxychloroquine (Plaquenil) 400 mg daily for 3 years. She complained of itching and redness of the eyelids, which she attributed to taking Plaquenil. For the last 5 years no anti-malarial therapy has been given.

In 1955 and 1956, the erythrocyte sedimentation rate, total and differential white cell counts, platelet count and haemoglobin concentration, the serum proteins (paper electrophoresis) and urine examination (microscopy) were normal. LE cells were not found in 1955 or 1958. The direct Coombs test was negative; the sheep cell agglutination test for rheumatoid factor (SCAT) was positive to a titre of 1:128. At no time has she had symptoms or signs suggestive of rheumatoid arthritis.

TABLE 1. Reactions to skin test with bacterial suspensions

Control	½ hr	4 hr	24 hr
Staph. albus	Erythema 10 × 10 Wheal 4 × 5	6 × 6*	5 × 5*
Staph. aureus	—	7 × 7*	18 × 15*
Strep. Lancfield Group G	—	—	—
Strep. salivarius	—	—	—
Strep. viridans	—	—	—

Results expressed as diameters (mm).

* Areas of erythema and induration.

In 1958, she developed purpura due to the drug carbromal, and in the same year palmar eczema. The latter has recurred a number of times since. Patch tests with 2·5% nickel sulphate, rubber additives and 5% ammonium thioglycollate were negative but she developed a reaction to adhesive plaster.

In 1963, an osteotomy was performed for hallux valgus and a few days later a severe relapse occurred of the lesions on the face, neck and upper limbs. These persisted until 1964 when she was treated with 0·025% betamethasone valerate (Betnovate) locally under polythene occlusion. The following laboratory investigations were performed and found to be normal: serum protein, total and differential white cell counts, haemoglobin concentration, ESR, LE cell test. ANF, Wasserman reaction and the Coombs test were negative. The latex agglutination test for rheumatoid factors was positive, and the SCAT test titre was 1:256.

In December 1964, in the course of an investigation into the skin reactivity of lupus erythematosus patients, she received separate intradermal injections of her own mononuclear cells, and granulocytes separated according to the method described by Valelzidis & Turk (1966). Each injection contained $7{\cdot}5 \times 10^6$ cells in a volume of 0·1 ml. She gave no reaction to her own mononuclear cells, but the granulocytes produced a wheal 8 mm in diameter, surrounded by an erythematous flare of 39 mm in diameter, maximal at 30 min after injection. No delayed reactions were seen. She also received intradermal tests with 0·1 ml of the following dead bacteria: *Staphylococcus aureus*, *Streptococcus* (*Lancefield Group G*), *Streptococcus*

salivarius, *Streptococcus viridans* and 0·05 ml of *Staphylococcus albus*. These suspensions all contained 5×10^6 bacteria/ml and were obtained from Bencard Allergy Unit, Beecham Research Laboratories, Brentford. They contained 0·5% phenol as preservative. She was also tested with a control solution containing the preservative only. The results are shown in Table 1. It can be seen that she developed an immediate type hypersensitivity to *Staph. albus*, and a delayed hypersensitivity reaction to *Staph. aureus*. The delayed hypersensitivity reaction faded within a week.

Six months after these intradermal tests, the patient had a sore throat and pyrexia. Next day the skin lesions on her face, neck and hands had relapsed and she developed a round, red patch at the site of the *Staph. aureus* injection into the anterior surface of the forearm. By the

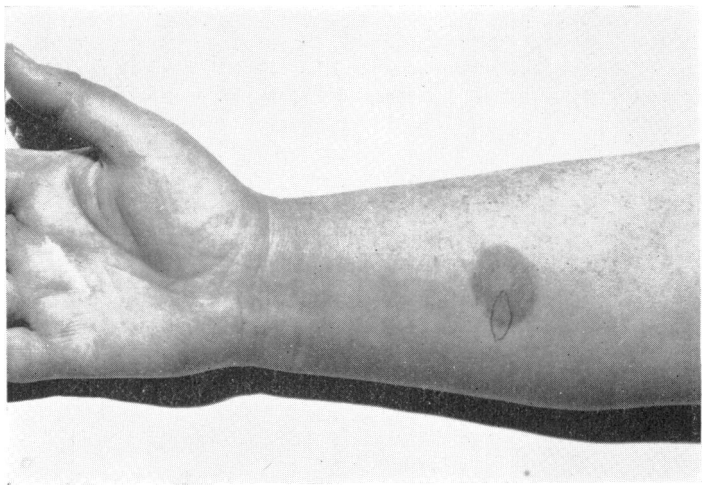

FIG. 2. Experimental *Staph. aureus* injection site, showing transformation from delayed hypersensitivity reaction to discoid lupus erythematosus. Site of biopsy indicated by pencil line.

time she was seen at the clinic 10 days later, she had a shallow round ulcer (30 mm diameter) at the injection site. According to the patient two similar flare-ups of the *Staph. aureus* injection site had occurred previously, about 2 and 4 months after the intradermal injections, during upper respiratory infections. The sites of inoculation with *Streptococci*, and the site of the immediate positive reaction to *Staph. albus* were at no time affected.

Seven months later, during an influenza-like illness, she developed erythema and induration followed by a large bulla (20 mm diameter) at the site of the original injection of *Staph. aureus*. A throat swab yielded a modest growth of normal flora and a nasal swab culture produced a pure growth of *Staph. aureus*. Ten days later the lesion was scaly and erythematous and this persisted for 2 months. A biopsy of this lesion (Figs. 2, 3 and 4) showed oedema of the subpapillary zone and an inflammatory infiltrate composed of lymphocytes and histiocytes in the upper dermis. Degenerative changes were present in the basal layer accompanied by hyaline body formation, compatible with lupus erythematosus. The biopsy was also examined by immunofluorescence. Direct application of anti-human globulin conjugate showed a faint continuous line of fluorescence just beneath the epidermis and compact small deposits in scattered areas at the dermal-epidermal junction as described by Tan & Kunkel (1966). Anti-β_{1C} conjugate stained only the discreet almost spherical aggregates scattered between the dermis and epidermis. There was no fluorescence of the nuclei in the biopsy and no deposits in the

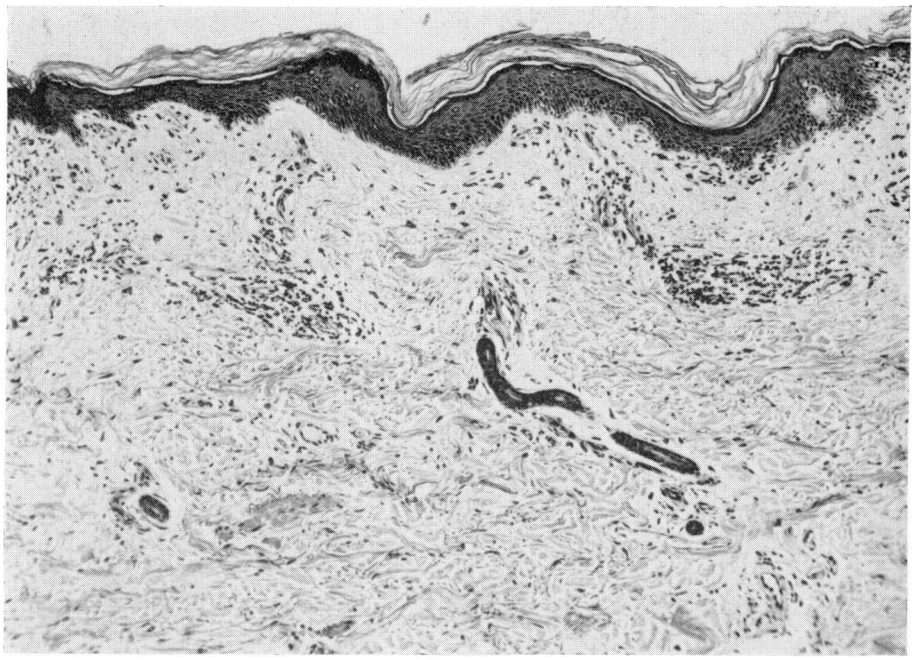

FIG. 3. Skin biopsy stained with haematoxylin and eosin, showing round-cell infiltration along vessels and oedema in upper corium. × 58.

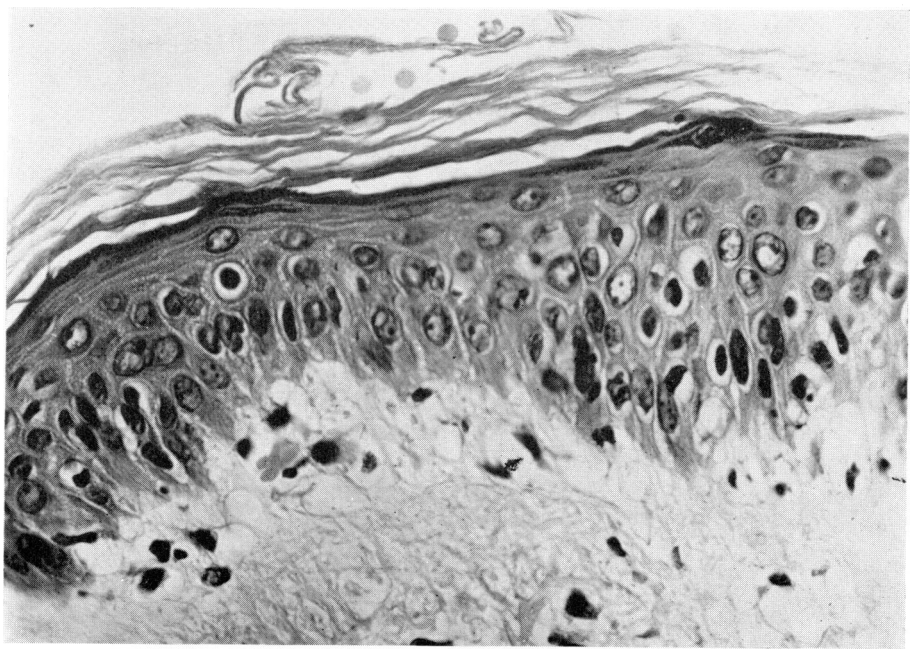

FIG. 4. High power view of biopsy showing marked oedema at dermal epidermal junction and hyaline bodies. × 290.

dermal vessels. An attempt was made to locate staphylococcal antigen in the lesion by application of a mixed anti-staphylococcal rabbit serum followed by anti-rabbit γ-globulin fluorescent conjugate. No specific staining was observed.

The patient's serum at that time gave a weak ANF reaction by indirect immunofluorescence and she had a trace of anti-thyroglobulin (TRC 1/40) probably related to her past thyrotoxicosis (Shrank & Doniach, 1964). Since many of her infections had been treated with tetracycline, she was tested for sensitivity to this drug by intradermal injection of 10 and 1 μg of methylenelysine (Lymecycline) (Whitby & Black, 1964). She gave no reaction to either injection and the *Staph. aureus* site at no time reacted to courses of tetracycline.

In the past few months, the chronic discoid lesions are still activated by infections but the *Staph. aureus* injection site has remained quiescent and shows only residual pigmentation.

DISCUSSION

This patient with chronic discoid LE shows several unusual features. The only evidence of systemic activity was the presence of high titre rheumatoid factors in the absence of arthritis. She also illustrates the overlap between LE and organ-specific autoimmune disease (Hijmans *et al.*, 1961; Shrank & Doniach, 1964; Doniach & Roitt, 1965). Furthermore, she had skin allergy to several chemical compounds. Repeated activation of discoid lupus in response to upper respiratory infections is unusual, though sunlight is a well-known precipitating factor.

After an experimental intradermal injection of *Staph. aureus*, this patient developed a typical 'delayed hypersensitivity' reaction and the organism was cultured from her nose. During subsequent infections, she developed a 'flare up' of the site of the original delayed reaction to *Staph. aureus* in the skin as well as exacerbations of her LE. On one occasion the 'flare up' persisted, and gradually changed over a period of 6 weeks into a patch of discoid lupus erythematosus. This was confirmed both by conventional histology and the fluorescent antibody technique. The suspicion that the deposits of immune complexes demonstrated in the skin contained the *Staph. aureus* antigen could not be substantiated with the available reagents.

The question that arises from this case is whether discoid lupus erythematosus could be a manifestation of a prolonged state of delayed hypersensitivity in the skin. This patient and many others with discoid LE have been skin tested with tuberculin and have shown marked delayed hypersensitivity reactions without developing a patch of LE at the site of the reaction. This patient developed a 'flare up' of the original skin test at a time when specific antigen might be present in the blood stream and could react with sensitized cells retained by subliminal residue of antigen at the old reaction site. The change over to discoid LE might have resulted from the injury caused by this reactivation, as occurs with sunlight and other stimuli. It could then be possible that the exacerbations of LE at other sites at the same time could be due to reaction between absorbed bacterial antigen and specifically sensitized cells at the site of old discoid lesions. The ultimate quiescence of the injection site might indicate that the concentration of immunologically active cells has dropped below the reactive levels, although her chronic lesions are still reactive. Another possibility is that the last infection was due to a different organism.

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