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Lupus Anticoagulant and the Skin

A Longterm Follow-up Study of SLE Patients with Special Reference to Histopathological Findings

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Skin manifestations were described in lupus anticoagulant (LA) positive and in LA negative SLE patients. Necrotic ulcers appearing at the beginning of the disease process characterized the 33 LA positive patients. Thirteen patients had a "peripheral vascular syndrome"; small leg ulcers of livedoid vasculitis type following deep venous thromboses, in 3 patients developing into pyoderma gangrenosum like ulcers and in 2 patients into pseudo-sarcoma Kaposi. The lesions were histologically characterized by capillary angiogenesis with extravasated red blood cells, sparse inflammatory cell infiltrates and microthromboses. Three patients had ulcers clinically and histologically resembling those seen in Degos' disease. Five patients had anetoderma showing elastic tissue depletion and microthromboses histologically. A different pattern of skin changes was seen in the LA negative patients. Our findings suggest that antiphospholipid antibodies play a pathogenetic role in the described skin manifestations of LA positive SLE patients. ***Key words: SLE; Anticardiolipin antibodies; Thromboses; Necrotic ulcers; Pseudosarcoma Kaposi; Anetoderma.***

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The occurrence of recurrent thromboses and fetal loss in patients with lupus anticoagulant (LA) and related antiphospholipid antibodies is well documented, especially in patients with systemic lupus erythematosus (1–6). Recently increasing interest has been focused on skin manifestations in these patients, but so far the majority of the reports have been anecdotal (7–14). We report a prospective study of skin manifestations in 33 LA positive SLE patients 23 of whom were also positive in the standard serological tests for syphilis. The findings were compared with those observed in 37 LA negative SLE patients. During the observation period various types of necrotic ulcers as well other skin changes, in addition to the SLE skin symptoms, were documented in the LA positive patients. The histological features characteristic to these cases were proliferating capillaries, microthromboses with sparse inflammatory cell infiltration, anetoderma and dermal necrosis compatible with that described by Degos.

MATERIALS AND METHODS

The series consisted of 33 SLE patients (26 women and 7 men) followed up for 5 to 22 years (mean 13.8 years) after the detection of the lupus anticoagulant (LA) at the Departments of Dermatology and Venereology, University of Helsinki and Karolinska Hospital, Stockholm. The patients were remitted to investigations because of skin lesions and/or positive serological tests for syphilis. The mean age of the patients at the onset of the first symptoms was 22.9 years (range 7 to 41 years) and the mean duration of the disease was 15.9 years (range 5 to 34 years). The patients have been examined on several occasions by one of us (E.S) Of the 33 patients 23 had chronic biological false positive (CBFP) seroreactions to syphilis (VDRL test positive > 6 months, negative TPHA and FTA-ABS tests). Altogether 11 of these patients were included in the previously published series (7, 15). The skin manifestations of the 33 patients were compared to those observed in our series of 37 LA negative SLE patients (32 women and five men) followed up for 7 up to 25 years (mean 15.7 years). The mean age at the onset of the symptoms was 20.7 years (range 8 to 41 years) and the duration of the disease 19.1 (range 10 to 30 years). During the follow up time the clinical and laboratory parameters included in the revised diagnostic criteria proposed by ARA (16) were applied to confirm the diagnosis of SLE. Altogether sixty skin biopsy specimens were taken from the different skin lesions. They were processed in paraffin, cut and stained with haematoxylin-eosine, toluidine blue and alcian blue.

Since 1969 our patients with definite or suspected SLE

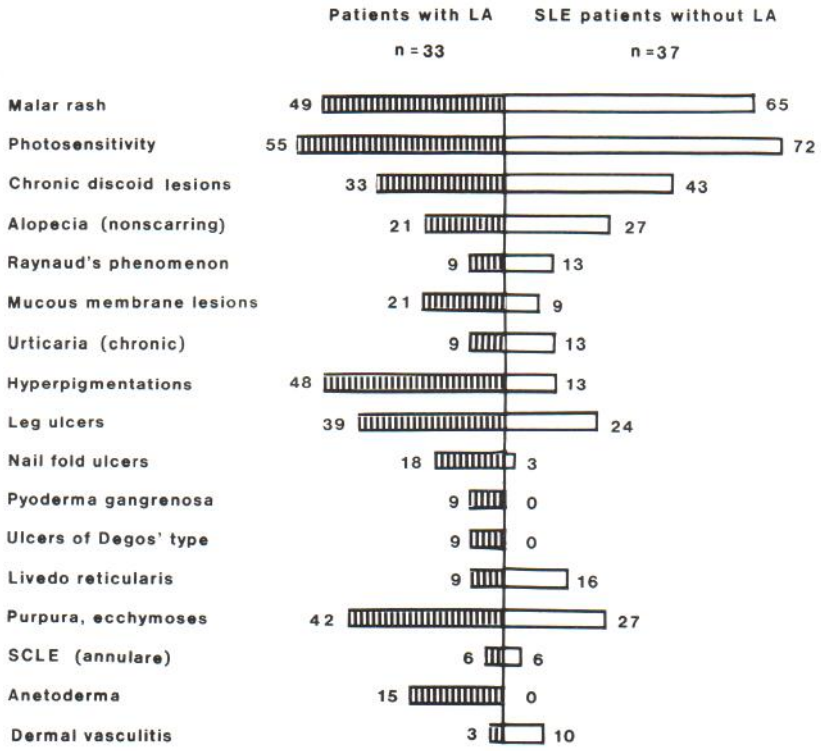

Fig. 1. The pattern of skin manifestations in the 33 LA positive and 37 LA negative SLE patients (numbers in %).

have been screened for LA with recalcification time (RT) (15). The RT was performed by incubating 0.2 ml of platelet poor plasma (PPP) with 0.2 ml of barbiturate-citrated buffer for 3 min at 37°C. The clotting time was measured after adding 0.2 ml of 0.33 M CaCI. If the RT of the tested plasma exceeded 150 sec, the test was continued by mixing the tested plasma diluted 1/10 in barbiturate citrate-buffered with normal pooled plasma, and by mixing the tested plasma with an equal volume of normal pooled plasma. The test was considered positive if the RT time of normal pooled PPP was prolonged for at least 20 sec when mixed with the tested plasma diluted 1/10 or by at least 30 sec when equal volumes were mixed.

Antinuclear antibodies (ANA), anti-dsDNA antibodies and complement C3 and C4 levels were examined repeatedly with standard methods (17). When last re-examined, the patients were screened for the occurrence anticardiolipin antibodies. Antibodies to cardiolipin (ACL) were measured by an enzyme-linked immunosorbent assay (ELISA) as previously described (18). The validity of the assay for IgG and IgM antibodies was ascertained with reference sera provided by the Lupus Research Laboratory of the Rayne Institute in London (19). No serum standard for IgA class ACL was available. The cut-off points for significantly raised levels of ACL were determined from the values of 190 middle-aged control subjects. The cut-off point at the 99th percentile level was 0.530 OD units for the IgG class (corresponding to 10 GPL units; the cut-off point in the earlier assay was 5 GPL units) and 0.318 OD units for IgM corresponding to 12 MPL units (the cut-off point in the assay of Harris and co-workers (19) was 3 MPL units) and 0.336 OD units for IgA class (no reference sera available).

RESULTS

Dermatological findings correlated to clinical data

The pattern of skin changes observed in the 33 LA positive SLE patients during the observation period differed from that seen in the 37 LA negative SLE patients (Fig. 1). The skin changes associated with LA activity are presented in Table 1 as they relate to some clinical and immunological data. At the time of re-examination 18 (75%) of the 24 patients still had LA which in Table 1 is shown to correlate with ACL. Increased amounts of ACL were found in 16/24 (67%) patients tested, seven in IgA, seven in IgG and nine in IgM class. Six of the patients with IgG-ACL had a history of or developed venous thromboses during the follow-up.

Dermatological and histopathological findings

"Peripheral vascular syndrome": presenting as small, extremely painful, livedoid vasculitis-like ulcers with a tendency to recur during the early summer months were seen in 13 LA positive patients. In all but two of these cases the ulcers developed soon after the first thrombosis in the early stage of the disease (Table I).

Table I. Lupus anticoagulant-associated skin manifestations as related to clinical and immunological data.

	No. of pat.	Sex F/M	Mean age at onset of the disease (range)	Mean dur. of disease (range)	Venous thrombs	ANA pos.** ≥100	C4 <0.10	ACL isotype			LA pos.
								IgG	IgA	IgM	
Total No of. patients	33	26/7	22.9 (7–41)	15.9 (5–34)	20	25***	22	7	7	7	18/24
Peripheral* vascular syndr.	13	6/7	23.4 (14–41)	2.6 (0–8)	13	7/13	7/13	7/7	2/7	1/7	7/7
Nailfold ulcers	6	4/2	22.7 (17–37)	10 (0–18)	5	3/6	5/6	3/5	2/5	1/2	4/5
Degos' type of ulcers	3	3/10	21.6	1.5	1	3/3	3/3	1/2	2/2	2/2	2/2
Pseudosarcoma Kaposi	2	0/2	20.5 (20,21)	20 (13,25)	2	1/2	1/2	2/2	1/2	2/2	2/2
Anetoderma	5	3/2	22.8	10.6	2	4/5	4/5	3/5	3/5	3/5	4/5
Purpura/ Echymoses	14	11/3	23.5 (14–39)	7.6 (0–34)	8	9/14	8/14	6/12	4/12	3/12	8/12
Livedo retic.	3	3/0	(7,39)	0	0	2/2	2/2	1/3	1/3	1/3	2/3

Dur. of the disease = duration of the disease in years at the time of detection of the respective symptom

* "peripheral vascular syndrome" = painful small, necrotic leg ulcers surrounded by dark pigmentation following deep venous thrombosis; 8 of them were included in the previous study (7).

** number of positive cases/number of patients examined.

*** five of the 8 ANA-negative patients had anti-dsDNA antibodies and 3 had SSA/SSB antibodies and constantly lowered complement C4 values.

The ulcers healed slowly leaving atrophic white scars with teleangiectasiae, surrounded by dark persistent hyperpigmentation. In three cases recurrent ulcers responded poorly to local as well as systemic treatment and progressed to large pyoderma gangrenosum-like ulcers, 4, 8 and 13 years after the first thrombosis respectively. In two patients lesions similar to *pseudosarcoma Kaposi* developed on both legs and feet 13 and 25 years after the first thrombosis (Table I).

Histopathologically both the early and late lesions were characterized by a scanty inflammatory cell infiltration but dominated by capillary angiogenesis and microthrombi. Nodular clusters of small capillaries intermingled with red blood cells, and large amounts of hemosiderin were seen throughout the dermis (Fig. 3). The pyoderma gangrenosum like ulcer lacked the typical undermined borders and there was no granulation tissue nor mixed inflammatory cell infiltration. In the Kaposi sarcoma-like lesions, capillary proliferation formed tumour-like nodules at all levels of dermis.

Leg ulcers were seen in 9 of the LA 37 negative patients and 5 of them had a history of deep venous thrombosis. The ulcers developed 2 to 12 years (mean 10.8 years) after onset of the disease. In three patients ulcers appeared 1 to 4 years after a deep venous thrombosis, and in two patients venous thromboses developed afterwards. In 4 patients large ulcers developed after a longstanding corticosteroid therapy – in two of them after a minor trauma on the skin showing steroid atrophy. Histological examination of four biopsy specimens showed capillary proliferation, a thickened capillary wall, but no proliferating capillary nodules or microthromboses.

Nailfold ulcers were seen in six LA positive and in one LA negative patient. In four of the LA positive patients the ulcers were associated with peripheral vascular syndrome (Fig. 2). Three LA positive patients presented with ulcers of *Dego's type*; small painful ulcers on the trunk and palms leaving porcelaine white scars (Fig. 4) and in on case appearing linearly on one overarm and shoulder on the sclerodermoid skin. Histological examination revealed a

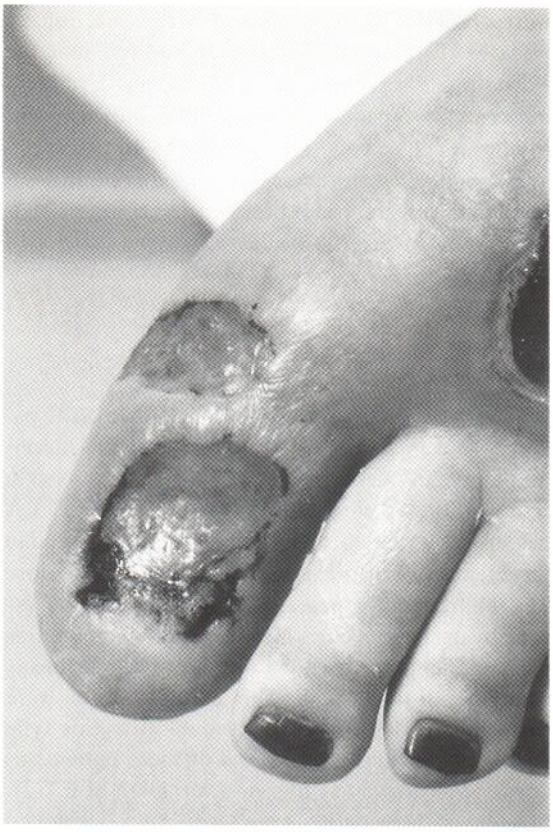

Fig. 2. A 24-year old woman initially presenting with "peripheral vascular syndrome"; recurrent deep venous thromboses, painful necrotic ulcers healing with atrophic scars with hyperpigmented borders. At re-examination she was found to have migratory superficial thrombophlebitis, nailfold ulcers and large necrotic ulcers on the dorsum of her feet.

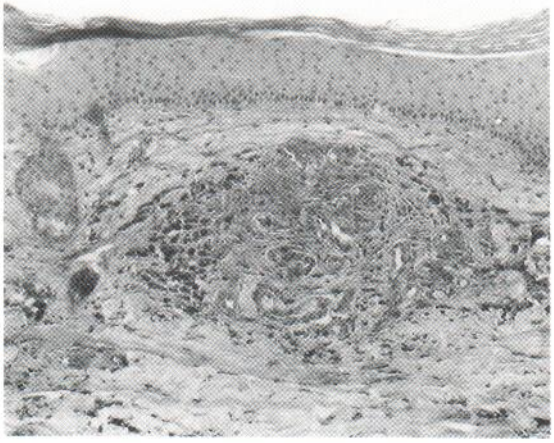

Fig. 3. Biopsy of the pseudosarcoma Kaposi like lesion. There are numerous nests of tighly packed capillaries in the upper dermis. Large amounts of hemosiderin and only a few inflammatory cells are seen around the capillaries (HE ×100).

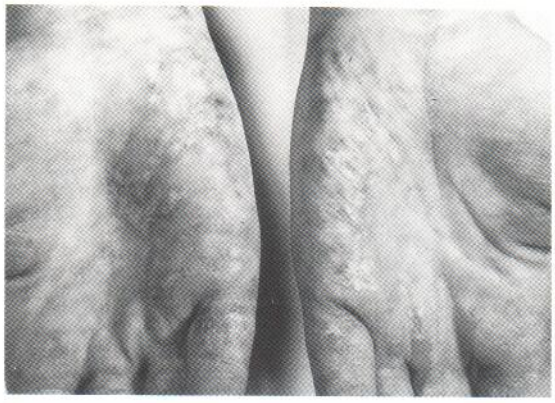

Fig. 4. Porceline white atrophic scars with red slightly indurated edges on the palms of the patient with Degos' type of ulcers.

superficial necrosis which covered a wedge-shaped homogenization of collagen elongating deep to the bottom of the dermis (Fig. 5).

Lymphocyte infiltration formed clusters deep in the dermis, and muscular blood vessels were thickened. Some were occluded and homogenized and surrounded by lymphocytes. There were large amounts of Alcian blue positive glycosaminoglycans. Marked capillary proliferation, with abundant extravasation of red cells but no inflammatory cells, was seen on the border of the subcutis. In some of the small capillaries, microthromboses were seen, and lymphocytes were found occasionally. *Livedo reticularis.* Three LA positive patients had red to violaceous non indurated lesions, one with reticular and two with striaform pattern. The lesions were in all

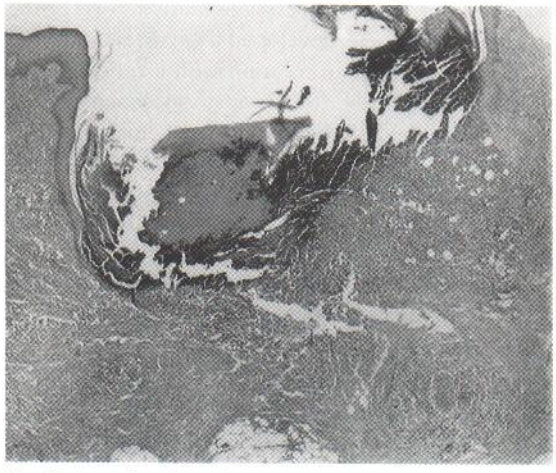

Fig. 5. A wedge-shaped necrosis of the upper dermis, homogenous collagen, clusters of lymphocyte infiltrates and marked capillary proliferation (HE ×260).

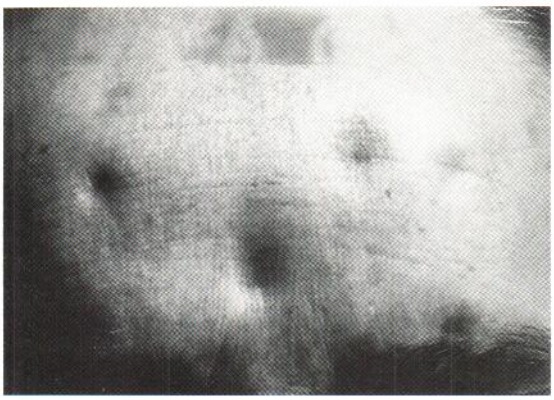

Fig. 6. A 30-year-old woman who developed anetoderma-like lesions on her forehead during her fourth pregnancy which ended in miscarriage at 8 weeks.

cases present at the time of the detection of the lupus anticoagulant. Histological examination of the lesions did not reveal signs of vasculitis. Capillary proliferations, microthromboses and extravasation of red blood cells were a common finding in the biopsy specimens taken from livedo reticularis lesions as well as specimens from purpura and ecchymoses. Livedo reticularis was observed in 8 of the LA negative patients; in five of them present at the onset of the disease. Two of them were teenagers and the changes vanished in adulthood. Biopsy specimens showed vasculitis in two of the 8 patients.

Malar rash or chronic discoid lesions were the most frequent initial skin manifestations in the patients. Six of the LA positive patients showed long-standing indurated lesions, which healed without scars but left a dark hyperpigmentation. Two of the LA positive patients developed a persistent dark red to violaceous papular eruption with a reticular pattern. Histologically, the biopsy specimens taken from the lesions of the discoid erythematosus type displayed the characteristic epidermal changes, but the dermis contained unusually large amounts of acid mucopolysaccharides, and capillary angiogenesis dominated in 3 specimens.

Anetoderma. Five patients presented a clinical picture of anetoderma. In 2 of the 3 women red to violaceous, changes 2 to 4 cm in diameter, were noted on the dorsal side of the upper arms present at the onset of the disease. In the third patient small anetoderma-like depressions appeared on the forehead during her second pregnancy (Fig. 6). Both men had numerous changes on the trunk; small, atrophic white depressions 0.2 to 0.3 cm in diamater were observed 15 to 18 years after the onset of the disease. Histological examination showed that the elastic tissue was depleted in the upper dermis: in the same area capillaries were filled with microthromboses (Fig. 7) and red blood cells. In two specimens giant cells with increased amounts of glycosaminoglycans were found between the collagen bundles. None of the LA negative patients developed anetoderma.

DISCUSSION

A long-term follow-up of 33 LA positive SLE patients showed that a variety of skin manifestations developed in these patients. The pattern of skin changes differed clearly from that seen in our 37 LA negative SLE patients and also from that reported in the literature (20). The most characteristic feature was the frequent appearance of vascular lesions, especially necrotic ulcers which were seen in two thirds of the patients. Clinically 4 different types of ulcers could be distinguished: The earliest ulcers were small painful leg ulcers of livedoid vasculitis type described previously by us in 8 of these patients as "*peripheral vascular syndrome* a variant of SLE" (7). In some of these patients the ulcers later developed into either large *pyoderma gangrenosum like* ulcers (second type) or into sarcoma-Kaposi like nodulus. Histologically they all presented the same capillary proliferation with microthromboses but without inflammatory cells as has been described previously (7, 10, 12). The marked capillary proliferation which

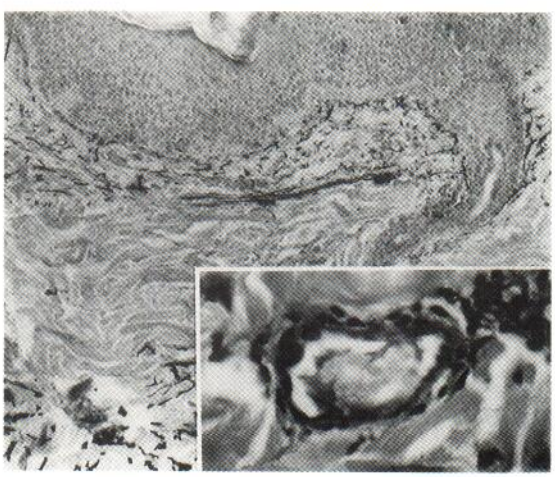

Fig. 7. Biopsy from an anetoderma lesion showing superficial lack of elastic fibers (Weigertresorcin-fuchsin ×600). Inset: microthrombosis in upper dermis (HE × 1400).

is characteristic but not specific has also been described as acroangiodermatitis in connection with venous insufficiency (21) and with arterio-venous fistulae (22). The clinical appearance has been compared with sarcoma Kaposi and named pseudosarcoma Kaposi or a simulant of Kaposi's sarcoma (23). As far as we know, LA has not been investigated in these cases. Recently attention has been focused on the differential diagnosis between acroangiodermatitis and AIDS-related Kaposi's sarcoma. None of our patients were HIV antibody positive. In a study of 520 SLE patients Tuffanelli and Dubois noted leg ulcers in 5.6% of the patients, but in contrast to our LA-positive patients none of their patients presented with leg ulcer as the initial complaint (20). None of our 9 LA negative patients developed leg ulcer as an initial sympton. The third type of ulcer appearing early was that of *Degos' type*. It appeared in association with LA, as first described by Englert and coworkers (8), but has not been previously described in linear scleroderma or in association with anetoderma, as in our series. In one biopsy specimen taken from a lesion which was clinically of Degos' type, we found an obliterating arteritis under the wedge-shaped collagen necrosis. This was also connected with a proliferating capillaritis in the upper levels of the dermis. The histopathological examination of sclerodermoid skin with ulcers revealed a similar homogenization of connective tissue with or without lymphocytes. it is possible that in both cases there is a similar mechanism which causes the gradual change from sclerodermoid ulcer to a necrotic hyalinized ulcer of Degos' type. Proliferating capillary nodules were found also in the ulcers of sclerodermoid type. None of these biopsy specimens were taken from the stasis area. The fourth type was the *nailfold ulcers* which developed late in the disease process and had a tendency to enlarge to extensive necrotic ulcers.

As far as we know anetoderma has not been reported previously in patients with LA. It is known as an uncommon cutaneous disorder which has been reported in association with SLE, syphilis or as an idiopathic disease (24). The histological picture of our cases differed from the classical anetoderma by the presence of giant cells, microthromboses and accumulation of glycosaminoglycans. Giant cells were found also in some of the cases reported by Venencie and co-workers (24, 25) but in their series Alcian blue positive material or microthromboses were not present. Several studies have recently demonstrated an association between antiphospholipid antibodies and livedo reticularis (26, 27, 28) but in our series livedo reticularis was a rare finding. According to our experience, this skin manifestation is easily overdiagnosed by including physiological cutis marmorata which is often seen in young individuals. Cutis marmorata is accentuated in cold and disappears on warming. It is also seen in patients receiving corticosteroids as due to decreased vascular tonus (29, 30). Livedo reticularis caused by cryopathies and hyperviscosity states should also be excluded (29, 30).

It has been confirmed in previous studies that SLE patients with lupus anticoagulant and/or anticardiolipin antibodies have a high risk of developing venous and/or arterial thromboses, which on the other hand have been connected with necrotic ulcers, especially leg ulcers. Altogether 61% of our LA positive SLE patients had a history of venous thrombosis or developed deep venous thrombosis during the follow-up time. It must be pointed out, however, that our series included patients who entered the study because of chronic biological false positive seroreactions (CBFP) for syphilis. In a previous study we found that deep venous thromboses occurred in 35% of LA positive CBFP reactors and in 14% of LA negative CBFP reactors (15). At re-examination 75% of our LA positive SLE patients were still LA positive and the occurrence of LA seemed to correlate with increased levels of ACL of the IgG isotype. The frequency of these antibodies was highest in the patients presenting the "peripheral vascular syndrome". The clinical picture, of these patients when entering the study, especially of the male patients, corresponded to that presented as primary antiphospholipid syndrome and SLE was diagnosed during the follow-up (6, 28).

On the basis of this study, it thus seems that different types of necrotic ulcers including pseudosarcoma Kaposi and pyoderma gangrenosum-like changes which histologically show collagen changes together with capillary proliferation and/or microthromboses should be included in the criteria of the antiphospholipid syndrome, and we would like to add anetoderma; elastic tissue depletion associated with microthromboses. Livedo reticularis seems to be more unspecific and difficult to evaluate because of the apparent lack of definite diagnostic criteria. Dermatological symptoms in patients with antiphospholipid antibodies seem to be manifestations of either vascular or connective tissue reactions. The pathomechan-

isms behind the "antiphospholipid syndrome" are still unknown, even though inhibition of prostacyclin production, inhibition of protein C activation and defect of free protein S have been suggested to play a role in the formation of thromboses (6).

In conclusion, the presence of LA and/ACL should be examined in all cases with small necrotic ulcers with hyperpigmentation, with pseudosarcoma Kaposi or pyoderma gangrenosum as well as in ulcers of Degos' type and anetoderma.

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