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Dermatologic Manifestations of the Antiphospholipid Syndrome

Two Hundred Consecutive Cases

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Objective. **To describe dermatologic manifestations of the antiphospholipid syndrome (APS) and to investigate possible correlations between livedo reticularis and other APS manifestations.**

Methods. **We conducted a single-center study of 200 consecutive patients with primary or systemic lupus erythematosus–related APS. To qualify for the study, patients had to fulfill clinical and laboratory criteria from the most recent international consensus statement on classification of definite APS. Dermatologic manifestations were systematically evaluated by a dermatologist. Only dermatologic lesions that may be related to APS were included in the analyses. Correlations between livedo reticularis and other APS manifestations were determined using Fisher's 2-tailed, chi-square, and nonparametric Mann-Whitney tests.**

Results. **Dermatologic manifestations were noted in 49% of the patients and were the presenting manifestations in 30.5%. Livedo reticularis was the most frequent manifestation, observed in 25.5% of the patients. Livedo reticularis was shown to be significantly associated with cerebral or ocular ischemic arterial events (odds ratio [OR] 10.8, 95% confidence interval [95% CI] 5.2–22.5), seizures (OR 6.5, 95% CI 2.6–16), all arterial events (OR 6, 95% CI 2.9–12.6), heart valve abnormalities detected on echocardiography (OR 7.3, 95% CI 3.6–14.7), and arterial systemic hypertension (≥160/90 mm Hg) (OR 2.9, 95% CI 1.5–5.7). Conversely, it was observed with decreased frequency in patients with only venous thrombosis (OR 0.2, 95% CI 0.1–0.5).**

Conclusion. **The dermatologic manifestations of APS are frequently the presenting feature of the syndrome, and livedo reticularis is significantly associated with the arterial subset of APS.**

Since the first description of antiphospholipid syndrome (APS) in 1983 (1), a wide variety of dermatologic manifestations of the syndrome have been described. They have been reported to occur in 4–55% of patients with APS, depending on the series (2–5). The dermatology literature contains only reports of small series or isolated cases of these lesions (6). The present study was undertaken to analyze dermatologic manifestations in 200 patients with APS and to investigate possible correlations between these dermatologic lesions and other APS manifestations.

PATIENTS AND METHODS

Consecutive patients with primary APS or systemic lupus erythematosus (SLE)–related APS, all of whom were seen at our connective tissue disease clinic, were studied retrospectively. To qualify for enrollment in the study, patients had to fulfill clinical and laboratory criteria for definite APS as defined in the consensus statement developed at the Eighth International Symposium on Antiphospholipid Antibodies (7). All patients had vascular thrombosis and/or pregnancy morbidity associated with persistent lupus anticoagulant (LAC) and/or anticardiolipin antibodies (aCL). LAC was usually screened by measurement of activated partial thromboplastin time and diluted thromboplastin time, and confirmed by mixing studies and demonstration of phospholipid dependence. IgG and IgM aCL were measured by solid-phase immunoassay with commercial enzyme-linked immunosorbent assay kits (Biomedical Diagnostics, Marne la Vallée, France). A patient was considered to be positive for aCL if the results were >3 SD above the mean in normal controls on at least 2 occasions. Positive aCL results were divided into low-positive

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Table 1. Characteristics of the 100 consecutive patients with primary APS and 100 consecutive patients with SLE-related APS*

	Primary APS	SLE-related APS	All APS
Female/male (ratio)	79/21 (3.8)	82/18 (4.6)	161/39 (4.1)
Age at diagnosis, mean (range) years	34 (12–79)	29 (12–63)	32 (12–79)
Arterial thrombosis	30	30	60
Venous thrombosis	40	41	81
Arterial and venous thrombosis	13	18	31
Sole microcirculatory thrombosis	4	6	10†
Sole obstetric morbidity	13	5	18

* Except where indicated otherwise, values are the number of patients. APS = antiphospholipid syndrome; SLE = systemic lupus erythematosus.
† One renal, 9 skin.

(15–25 IgG phospholipid units [GPL units] or IgM phospholipid units [MPL units]), medium-positive (26–80 GPL or MPL), or high-positive (>80 GPL or MPL), as in previous studies (8). Only patients found to have medium- or high-positive aCL were included in the present study.

The presence of dermatologic manifestations was evaluated systematically. Most of the patients were examined by an experienced internist (JCP). All who exhibited skin manifestations were examined by a senior dermatologist (CF). For purposes of this study, only dermatologic lesions that might be related to APS were recorded. A lesion was considered to be possibly related to APS based either on data from the literature (livedo reticularis, subungual splinter hemorrhages, thrombocytopenic purpura, anetoderma) (6,9), confirmation of thrombosis by imaging or Doppler studies (distal thrombosis, superficial thrombophlebitis, post-phlebitic ulcers), or histopathologic findings (extensive cutaneous necrosis, circumscribed cutaneous necrosis, pseudovasculitis purpura). Physiologic cutis marmorata was not recorded or, when recorded, was not considered to be related to APS. In the first 26 patients with livedo reticularis (15 with primary APS and 11 with SLE-related APS), 2 biopsy specimens 1 cm in diameter were obtained, from the center of the livedo and at the violaceous netlike pattern. Systematic biopsy studies were performed in all patients with extensive cutaneous necrosis, circumscribed cutaneous necrosis, anetoderma, and pseudovasculitis manifestations, regardless of the presence of livedo reticularis. All specimens were fixed in Bouin's liquid, conventionally processed, and embedded in paraffin. Serial sections were stained with hematoxylin/eosin/saffron and orcein. All tissue sections were reviewed retrospectively by 1 pathologist (FlP).

One hundred patients with primary APS and 100 with SLE-related APS were enrolled in the study. They were classified according to the type of APS event: arterial thrombosis, venous thrombosis, both venous and arterial thrombosis, sole obstetric morbidity, or sole microcirculatory thrombosis (Table 1). Some patients in the first 3 groups also had obstetric morbidity or microcirculatory thrombosis. Two patients with both venous and arterial thrombosis also had catastrophic APS resulting in mutiorgan failure. The mean ± SD duration of followup since the first APS event was 11.3 ± 6.3 years in the overall group of 200 patients (median 10 years), 9.8 ± 6.0 years in the arterial thrombosis subset (median 9 years), 13.1 ± 6.7 years in the arterial and venous thrombosis subset (median 13.1 years), 12.2 ± 6.3 years in the venous thrombosis subset (median 11 years), 10.4 ± 6.1 years in the obstetric morbidity subset (median 10 years), and 7.6 ± 6.0 years in the microcirculatory thrombosis subset (median 7 years).

Fisher's 2-tailed test and the chi-square test were used to compare qualitative data. The nonparametric Mann-Whitney test was used to compare quantitative data.

RESULTS

Clinical findings and correlates. Dermatologic manifestations were noted in 49% of the patients, and a dermatologic manifestation was the presenting symptom in 30.5% (Table 2). The overall frequency of dermatologic manifestations and the frequency of each individual dermatologic manifestation were not significantly different between the patients with primary APS and those with SLE related APS.

Livedo reticularis was the most frequent manifestation, observed in 25.5% of cases. It was the presenting feature of APS in 17.5% of cases. It was usually widespread (present on the limbs, but also on the trunk and/or the buttocks) and not infiltrated, with a fine irregular network. Figure 1A shows typical irregular livedo reticularis in a patient with SLE-related APS, and Figure 1B shows a regular physiologic cutis marmorata.

The prevalence of livedo reticularis was 46.6% in the subset of patients with arterial thrombosis, 35.5% in the subset with arterial and venous thrombosis, 8.6% in the subset with venous thrombosis, 11.1% in the subset with obstetric morbidity, and 3% in the subset with microcirculatory thrombosis. The higher prevalence of livedo reticularis in patients with arterial thrombosis was statistically significant ($P < 0.001$) and could not be explained by a longer duration of followup in the arterial thrombosis subset: there was no statistically significant difference in the duration of followup between patients in the arterial thrombosis, venous thrombosis, and ob-

Table 2. Dermatologic manifestations

	No. with manifestation (no. with manifestation as presenting symptom)*		
	Primary APS (n = 100)	SLE-related APS (n = 100)	All APS (n = 200)
Any	45 (36)	53 (25)	98 (61)
Livedo reticularis	31 (21)	20 (14)	51 (35)
Digital necrosis	3 (1)	12 (4)	15 (5)
Subungual splinter hemorrhages	4 (2)	6 (2)	10 (4)
Superficial venous thrombosis	4 (1)	6 (2)	10 (3)
Post-phlebitic ulcers	2 (1)	7 (0)	9 (1)
Circumscribed cutaneous necrosis	5 (5)	2 (2)	7 (7)
Thrombocytopenic purpura	1 (1)	6 (2)	7 (3)
Pseudovasculitis manifestations	4 (3)	2 (1)	6 (4)
Extensive cutaneous necrosis	1 (1)	3 (3)	4 (4)
Primary anetoderma	2 (0)	2 (0)	4 (0)

* There were no significant differences in the frequency of any dermatologic manifestation between the primary antiphospholipid syndrome (APS) group and the systemic lupus erythematosus (SLE)–related APS group.

stetric morbidity subsets. The followup of the subset of patients with both arterial and venous thrombosis was slightly longer than that of patients with only arterial thrombosis ($P = 0.02$) and was not significantly different from that of patients in the venous thrombosis or obstetric morbidity subsets. Followup of patients with only microcirculatory thrombosis was shorter than that of patients with arterial and venous thrombosis ($P = 0.02$) and patients with venous thrombosis ($P = 0.03$). There were no other statistically significant differences in the duration of followup between APS subsets. The mean ± SD duration of followup of patients with livedo reticularis (8.8 ± 5.6 years [median 9 years]) was lower than that of patients without livedo reticularis (12.0 ± 6.4 years [median 11 years]) ($P = 0.001$).

The investigation for possible correlations between livedo reticularis and other manifestations of APS (Table 3) showed a statistically significant association with cerebral or ocular ischemic arterial events, seizures, all arterial events, heart valve abnormalities detected on echocardiography, systemic hypertension (≥160/90 mm Hg), and Raynaud's phenomenon. Conversely, among the patient group as a whole, livedo reticularis was observed with less frequency in those with only venous thrombosis. Similar correlations were observed in the group with primary APS (except that the association of

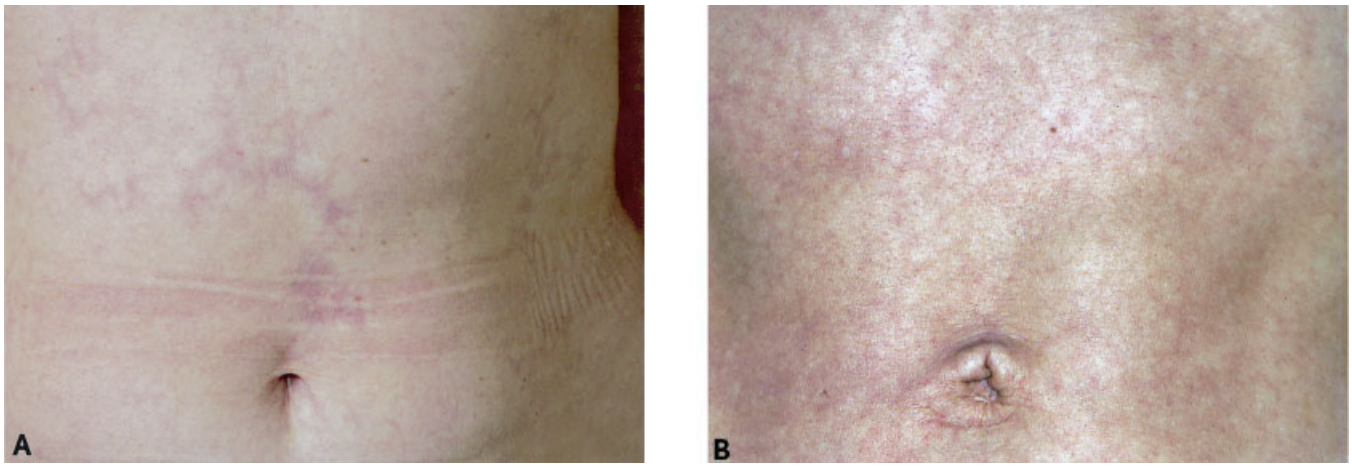

Figure 1. A, Fine livedo racemosa of the trunk in a patient with systemic lupus erythematosus–related APSantiphospholipid syndrome (APS). The fishnet reticular pattern is composed of broken circles. **B,** Physiological cutis marmorata in a subject without APS. The fishnet reticular pattern is composed of regular full circles.

Table 3. Correlates of livedo reticularis in all APS patients, patients with primary APS, and patients with SLE-related APS*

	LR+, %	LR−, %	OR	95% CI	*P*
Cerebral or ocular ischemic arterial events					
All patients	69	17	10.8	5.2–22.5	<0.0001
Primary APS	68	23	7.0	2.7–17.8	<0.0001
SLE-related APS	70	11	18.4	5.6–60	<0.0001
Seizures					
All patients	29	6	6.5	2.6–16	<0.001
Primary APS	19	8	3.0	0.9–10.9	0.09
SLE-related APS	45	5	15.5	4.1–59.2	<0.0001
Arterial events					
All patients	85	39	6.0	2.9–12.6	<0.0001
Primary APS	71	30	5.6	2.2–14.2	0.0002
SLE-related APS	85	39	9.0	2.4–33.1	0.0002
Heart valve abnormalities on echocardiography					
All patients	63	19	7.3	3.6–14.7	<0.0001
Primary APS	55	17	5.8	2.2–14.8	0.0001
SLE-related APS	75	20	12.0	3.8–37.9	<0.0001
Arterial systemic hypertension (≥160/90 mm Hg)					
All patients	43	21	2.9	1.5–5.7	0.0018
Primary APS	39	20	2.5	1.0–6.2	0.0521
SLE-related APS	50	21	3.7	1.3–10.3	0.0096
Venous thrombosis					
All patients	20	52	0.2	0.1–0.5	<0.0001
Primary APS	16	51	0.2	0.1–0.5	0.0011
SLE-related APS	25	54	0.3	0.1–0.9	0.0213
Raynaud's phenomenon					
All patients	49	28	2.4	1.3–4.7	0.006
Primary APS	42	10	6.4	2.2–18.4	0.0002
SLE-related APS	60	44	1.9	0.7–5.2	0.19

* APS = antiphospholipid syndrome; SLE = systemic lupus erythematosus; LR = livedo reticularis; OR = odds ratio; 95% CI = 95% confidence interval.

livedo reticularis with systemic hypertension and with seizures was not significant) and the group with SLE-related APS (except that the association with Raynaud's phenomenon was not significant).

The presence of livedo reticularis was associated with higher levels of IgG aCL (mean 161.6 GPL units in patients with livedo reticularis versus 82.1 GPL units in patients without; $P = 0.006$). In contrast, the levels of IgM aCL (mean 12.7 versus 19.7 MPL units, respectively) and prevalence of LAC (70.6% versus 60.8%, respectively) were similar in the presence or absence of livedo reticularis. No statistically significant variation of IgM aCL levels was observed among the different APS subsets (data not shown). Mean levels of IgG aCL were not significantly different among the arterial thrombosis, arterial and venous thrombosis, and venous thrombosis subsets (109.7, 145.4, and 86.1 GPL units, respectively). In contrast, comparison between all patients with arterial thrombosis and the group of women with only obstetric morbidity showed significantly higher levels of IgG aCL in those with arterial thrombosis (122.1 GPL units versus 54.7 GPL units; $P = 0.049$). No significant difference was observed between the venous thrombosis and obstetric morbidity subsets. The prevalence of LAC was similar in the arterial thrombosis, arterial and venous thrombosis, and venous thrombosis subsets (66.6%, 71.8%, and 65.4%, respectively). This prevalence was significantly lower in the obstetric mortality subset (27.7%) ($P < 0.01$).

The frequency of other dermatologic manifestations was too low to enable us to investigate statistically for possible correlations with other APS events. Digital gangrene was related to occlusion of large or medium-sized vessels confirmed by Doppler echocardiography or angiography. In 4 patients, this led to amputation of 1 or 2 digits. Multiple subungual splinter hemorrhages occurred concomitantly with arterial events or acute adrenal failure. Superficial phlebitis was mainly observed on the limbs. One patient had 5 episodes of superficial phlebitis of both legs, without any other APS event. Two types of ulceration were observed: post-phlebitic ulcers (4.5% of the patients), which were rarely a presenting feature, and ulcerations secondary to circumscribed cutaneous necrosis (3.5%), mainly localized on the lower

limbs and sometimes leading to atrophie blanche–like scars. These ulcers were the sole manifestations of APS in 5 cases, and a presenting feature in all 5.

Pseudovasculitis was usually purpuric and necrotic, and was frequently associated with circumscribed cutaneous necrosis of the legs (in 5 of 6 cases). In the absence of necrosis, vasculitis was diagnosed based on clinical findings, especially in 2 patients with SLE who developed, respectively, painful erythema and purpura of the fingers; these manifestations were considered to be related to APS based on the pathologic finding of thrombosis of the superficial dermal vessels without vasculitis. Extensive cutaneous necrosis was the sole manifestation of APS in 3 cases. One patient had a concomitant lupus flare with palpable purpura on the ankles, along with leukocytoclastic vasculitis and an extensive necrotic plaque of the thighs. Skin lesions of anetoderma were numerous (>10) and were localized predominantly on the upper half of the chest and arms. In this series, anetoderma was present only in patients with at least 1 arterial event.

Histologic findings. The histologic features of livedo reticularis were similar in patients with primary APS and those with SLE-related APS. In 19 of the 26 patients (73%) from whom 2 livedo biopsy specimens were available, no obvious pathologic change was detected despite careful examination of numerous serial sections.

Vascular abnormalities were noted in 1 of the 2 livedo biopsy specimens from each of the other 7 patients (4 with primary APS and 3 with SLE-related APS). Specimens with abnormalities had been obtained from the center of the livedo (4 cases) or from the violaceous fishnet (3 cases). Vascular changes involved small to medium-sized arteries (i.e., with a distinct lamina elastica interna) localized at the dermis–subcutis boundary or in the subcutis. In 3 cases, arteriolar lesions consisted of partial or complete occlusion of the arterial lumen by a cellular plug with numerous mononuclear cells. In 3 other cases, arterioles were shrunken and occluded by a fibrotic, acellular plug, and lamina elastica interna was deteriorated. Thrombosis of an arteriole of the subcutis was evident in only 1 case (in a patient with primary APS). Biopsy of pseudovasculitis lesions revealed thrombosis of the superficial dermal vessels, with a mild lymphocytic infiltrate. Thrombosis of the upper dermal blood vessels at the border of circumscribed skin necrosis was sometimes masked by extravasated erythrocytes and capillary angiogenesis, which led in 1 case to reactive angioendotheliomatosis. In 2 cases, 2 biopsies were necessary to detect thrombi in dermal vessels. In contrast, thrombi were evident in all dermal vessels from the border of the necrotic plaques. No microthrombosis could be detected in any anetoderma biopsy specimens.

Treatment. Frequently, livedo persisted despite long-term anticoagulation therapy (in 44 patients). New cases of livedo occurred despite anticoagulation therapy in 2 patients. In 5 patients, livedo disappeared after 2–5 years of followup although treatment remained unchanged and antiphospholipid antibodies (aPL) were still present. Livedo was less visible on suntanned skin. All patients with digital gangrene and widespread cutaneous necrosis received full anticoagulation therapy with heparin. In the 5 patients in whom spreading of necrosis persisted despite anticoagulation therapy, plasma exchange with pulse steroids was prescribed to prevent "aPL rebound." Iloprost was further added to the regimens of these 5 patients to increase the healing process, and long-term treatment with a high-intensity vitamin K antagonist (international normalized ratio [INR] ≥3) was instituted to prevent recurrence. In patients with isolated pseudovasculitis manifestations and circumscribed skin necrosis, low-dose aspirin and dipyridamole were initially prescribed. In 4 patients, painful skin necrosis persisted despite antiplatelet therapy, and long-term anticoagulation treatment as initiated for healing and prevention of recurrence.

DISCUSSION

The large variation in the reported prevalence of dermatologic manifestations (4–55%) in previous series of APS patients (2–5) is probably due to the lack of routine dermatologic examination of these patients. When dermatologic manifestations related to APS were systematically investigated in the present study, their overall prevalence was high (49%), and was similar in primary APS (45%) and SLE-related APS (53%). For purposes of this study, physicians at our institution were reminded regularly to check for any skin manifestations in their patients with APS; however, it is possible that some less evident skin lesions could have been overlooked, in which case the actual prevalence would be higher than reported herein.

Livedo reticularis was the most frequently observed dermatologic manifestation (25.5%), with a similar prevalence in primary APS (31%) and SLE-related APS (20%). It was a presenting manifestation in 17.5% of cases. In a cohort of 1,000 European patients with APS (5), the overall prevalence of livedo reticularis was found to be 24.1%, and it was higher in patients with SLE-associated APS versus those with primary APS

(36% versus 16%; $P < 0.001$), and in female versus male patients (26% versus 16%; $P < 0.005$). Livedo reticularis was a presenting manifestation in 20.4% of cases in that cohort (5). In our series, livedo reticularis was more prominent and troublesome in women than in men. When it was associated with circumscribed skin necrosis (in 3 of 7 patients with circumscribed necrosis), it was mainly localized on the lower limbs. When livedo reticularis was the sole cutaneous manifestation (Figure 1A), its clinical features, although nonspecific, were suggestive of APS. It was usually widespread, noninfiltrated, and localized not only on the limbs but also on the trunk and/or buttocks. In some patients with APS, livedo reticularis may be restricted to the hands and feet, at least initially (10). The fishnet reticular pattern is mainly irregular (livedo racemosa). On the trunk, the fishnet of the livedo is usually fine, in contrast to the large fishnet observed in aPL-negative patients with Sneddon's syndrome (8). This fine pattern may explain why it may be hidden by hair, especially in men.

The recent classification criteria for definite APS include noninflammatory microvascular thrombosis (7). Because this histologic feature was rare in the livedo biopsy specimens obtained in this study, we do not consider skin biopsy of livedo reticularis to be useful in patients with APS and did not perform biopsies in the last 25 patients. Therefore, a pathologic description could not be detailed in all patients with livedo reticularis. However, we believe the clinical feature of widespread noninfiltrated fine livedo racemosa might be included in future "minor criteria" for APS (11).

Reports of a strong association between livedo reticularis and cerebrovascular events in patients with SLE have appeared in the literature for more than 10 years (12–14). In 1965, this association, i.e., livedo reticularis and cerebrovascular events, was first documented in otherwise healthy people (15) and was designated as Sneddon's syndrome. A relationship between APS and Sneddon's syndrome was first documented by Hughes (1) and later confirmed by others (16,17). In the present series, livedo reticularis was found to be strongly associated not only with cerebrovascular events, but also with systemic hypertension and heart valve abnormalities. Conversely, its prevalence was low in patients with only venous events. Thus, livedo appears to be a good marker for the "arterial/arteriolar" APS subset.

Necrotic skin ulcerations in association with LAC were first reported in 1963 (18). Skin ulcers were observed in 5.5% of the 1,000 reported European patients with APS and were a presenting manifestation in 3.9% (5). In many series (4,19), they are not mentioned. A strong association between leg ulcers and aCL in patients with SLE has been reported; in some cohorts, the reported prevalence of aCL is as high as 87% in such patients (20). In a series of 115 consecutive patients hospitalized in a dermatology unit for leg ulcers, aCL were detected in 43% (21). In the present series, ulcers were detected in 8% of cases. They consisted of post-phlebitic ulcers and ulcerations resulting from circumscribed skin necrosis. Post-phlebitic ulcers were observed in patients with recurrent phlebitis of the leg, after many years of followup. In contrast, circumscribed skin necrosis is frequently an early feature of APS, often preceded by necrotizing purpura (22,23). In a series of 21 consecutive patients with atrophie blanche–like ulcers or livedoid vasculitis, aPL were detected in 4 (19%), of whom 1 had SLE-related APS and 3 had primary APS (24). Other prothrombotic factors may also be present (25). We did not observe large ulcers resembling pyoderma gangrenosum, although these have been reported in several cases (26,27).

The pseudovasculitis lesions mimic cutaneous vasculitis and may be misdiagnosed, especially in patients with SLE, if skin biopsies are not performed. They were the presenting manifestations in 2.6% of the 1,000 patients with APS in the European cohort and were observed in 3.9% of these patients during the course of the disease (5). Different features have been reported, i.e., purpura, small erythematous or cyanotic lesions on the hands and feet (28), papules or nodules on the limbs, ears, neck, or thighs (29–32), and localized necrotic areas of the neck and anterior chest (33).

Clinical features of widespread superficial cutaneous necrosis in APS are similar to those observed in other thrombophilic states, such as protein C or protein S deficiencies, monoclonal cryoglobulinemia, or cryofibrinogenemia. In some cases, these biologic abnormalities, present in association with aPL, may contribute to the thrombotic process (34,35). APS may be primary or associated with other disorders, such as SLE, rheumatoid arthritis, mycosis fungoides, or human immunodeficiency virus infection (36–39). Cutaneous necrosis was reported in 2.1% of the 1,000 patients in the European series (5). The onset is often acute, with extensive painful purpura followed by a black necrotic plaque with an active purpuric border and bullous lesions. The necrosis is usually localized on the limbs, head (cheeks, nose, ears), or buttocks. Histopathologic analysis of early purpuric lesions demonstrates diffuse skin vessel thrombosis. In 1 reported case, both focal thrombosis and a reactive angioendotheliomatosis contributed to the angiooccclusive pathology (40).

Multiple subungual splinter hemorrhages were noted in 5% of the patients in the present study. In APS, their sudden onset on multiple fingers frequently occurs concurrently with other worrisome thrombotic events, therefore leading to a probable underestimation, as illustrated by the 0.7% prevalence noted in the European study (5,41). In 1 patient, it was coincidental with catastrophic APS. Skin lesions, characterized by widespread microvascular occlusions involving multiple organs simultaneously, are frequently observed in catastrophic APS (70% of cases). Livedo reticularis, acrocyanosis, large cutaneous necrosis, palmar erythema, digital gangrene, and ischemic ulcers have been reported to occur in this condition (42).

Primary anetoderma is a rare disorder characterized clinically by a circumscribed area of slack skin with macular depressions or outpouchings. We have previously reported that in patients with SLE, these skin lesions were always associated with aPL (9). Arterial, venous, or obstetric APS events have been reported in this context (43). Primary anetoderma may also be observed in association with other prothrombotic abnormalities (9). Microthromboses were reported in only 1 case (44). It is conceivable that hypoxia-reoxygenation may trigger a local imbalance between metalloproteinases and their inhibitors, leading to the destruction of elastic tissue (9).

Thrombocytopenic purpura was found in 3.5% of the patients in the present study and was more prevalent in patients with SLE-related APS (6%) than in those with primary APS (1%). In the European APS cohort, severe thrombocytopenia ($\leq$30,000 platelets/mm^3) was also found more frequently in patients with SLE (5).

In decision-making with regard to the treatment of patients with skin lesions, both the dermatologic manifestations and the overall clinical situation must be considered. In addition to treating the acute condition, clinicians must consider whether long-term prophylactic therapy is indicated. In the absence of randomized controlled trials, therapy for dermatologic lesions remains empirical. Due to the retrospective nature of the present study, the efficacy of various treatment regimens could not be compared.

Widespread cutaneous necrosis and digital gangrene are major thrombotic events that require full anticoagulation therapy with heparin. If these skin lesions continue to spread despite anticoagulation therapy, iloprost and/or plasma exchange may be prescribed; these have been reported to be successful in isolated cases (38,45). When plasma exchange is administered, steroids and/or cytotoxic agents should probably be added to the regimen to prevent "aPL rebound," as occurs in catastrophic APS (46,47).

No treatment has been proven to be effective for livedo reticularis, which, in our experience, may extend or appear despite anticoagulation or antiplatelet therapy. Livedo reticularis is less visible on suntanned skin, but sun exposure is not recommended in patients with SLE, and we think it should be proposed only to aPL-negative patients desiring to mask a troublesome livedo.

For other isolated skin lesions such as circumscribed necrosis or pseudovasculitis, combination therapy with low-dose aspirin and dipyridamole has been reported to be effective in some cases (31,32). If these lesions recur or extend despite antiplatelet treatment, anticoagulation is usually prescribed. One report describes the successful use of fibrinolytic agents and heparin in the treatment of refractory nonhealing cutaneous ulcers (48).

Preventing the recurrence of skin lesions in APS depends not only on their severity, but also on the other features of the disease. There are no reported data concerning the frequency of recurrence of skin vessel thrombosis. The literature contains only 1 report of a patient who had 2 separate episodes of widespread cutaneous necrosis, each precipitated by surgical manipulation of the urinary tract in the presence of urinary tract infection (49). Because widespread cutaneous necrosis and/or digital gangrene are considered to be major thrombotic events, the current recommended treatment in such cases is long-term high-intensity warfarin (INR $\geq$3), as is used for patients with large artery thrombosis. It is unclear how recurrences of isolated "minor dermatologic manifestations" (i.e., circumscribed cutaneous necrosis, pseudovasculitis skin lesions, superficial thrombophlebitis) may be prevented. Antiplatelet therapy, such as low-dose aspirin (75 mg/day), is usually chosen as first-line treatment. Hydroxychloroquine also has well-documented antiplatelet effects and has been shown to reduce the risk of thrombosis both in SLE patients and in animal models of APS (50,51). However, in our experience, these treatments are rarely effective, and long-term anticoagulation is frequently required (24).

Regardless of the type of skin involvement, it is important to remove or reduce other risk factors for thrombosis or arterial wall lesions (52). For example, patients are advised to stop smoking, and women are counseled against the use of estrogen-containing pills. The potential benefit of treatment with statins (53) or angiotensin-converting enzyme inhibitors (54) needs to be determined, especially in patients with livedo.

In conclusion, dermatologic manifestations may be the presenting feature of the antiphospholipid syndrome. They are extremely diverse and heterogeneous, ranging from minor signs to life-threatening conditions such as widespread cutaneous necrosis. Livedo reticularis is strongly associated with the arterial subset of APS. Rigorous studies are needed to determine the optimum means to manage dermatologic manifestations in APS and to assess the possible benefit of recently developed antithrombotic agents.

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