Cutaneous manifestations of antiphospholipid syndrome: a review of the clinical features, diagnosis and management

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ABSTRACT

Antiphospholipid syndrome is a relatively recent systemic autoimmune disorder defined by thrombotic events and/or obstetric complications in the presence of persistent elevated antiphospholipid antibodies. It is characterized by a wide spectrum of clinical presentations and virtually any organ system or tissue may be affected by the consequences of vascular occlusion. Diagnosis is sometimes difficult and although classification criteria have been published and revised there remain ongoing issues regarding nomenclature, expanding clinical features, laboratory tests and management and much still has to be done. Cutaneous manifestations are common and frequently the first sign of the disease. Although extremely diverse it's important to know which dermatological findings should prompt consideration of antiphospholipid syndrome and the appropriate management for those patients. Much has been debated about when to consider antiphospholipid syndrome and consensus still does not exist, however in spite of being a diagnostic challenge clinicians should know when to look for antiphospholipid antibodies since an early diagnosis is important to prevent further and serious complications. In this article we focus on the cutaneous features that should raise suspicion on the presence of antiphospholipid syndrome and on the complex management of such patients. Many other dermatological signs related to this syndrome have been described in the literature but only occasionally and without consistency or statistic impact and therefore will not be considered here.

Keywords: Antiphospholipid Syndrome; Skin; Dermatology; Review; Diagnosis.

RESUMO

O síndrome antifosfolipidico é uma patologia auto-imune relativamente recente definida por eventos trombóticos e/ou complicações obstétricas na presença de anticorpos antifosfolípido elevados persistentes. Caracteriza-se por um vasto leque de apresentações clínicas e virtualmente qualquer sistema orgânico ou tecido pode ser afectado por oclusão vascular. O diagnóstico é por vezes difícil e, apesar de critérios de classificação terem sido publicados e revistos, muitas dúvidas persistem relativamente à nomenclatura, características clínicas, testes laboratoriais e abordagem destes doentes. As manifestações cutâneas são comuns e, frequentemente, o primeiro sinal da doença. Apesar da grande variabilidade, é importante reconhecer os achados dermatológicos que devem levantar a suspeita de um síndrome antifosfolipidico, assim como a abordagem adequada destes doentes. Muito tem sido debatido sobre quando considerar o diagnóstico desta entidade, não havendo ainda consenso neste assunto; no entanto, apesar de ser um desafio diagnóstico, é importante saber quando investigar a presença de anticorpos antifosfolípidos, uma vez que um diagnóstico precoce é crucial para prevenir complicações futuras graves. No presente artigo os autores descrevem as manifestações dermatológicas que devem fazer considerar o diagnóstico com enfoque na abordagem complexa destes doentes. Têm sido descritas na literatura muitas outras alterações cutâneas relacionadas com esta entidade, no entanto, apenas de forma ocasional e sem consistência ou impacto estatístico, pelo que não serão consideradas.

Palavras-chave: Síndrome Antifosfolipidico; Pele; Dermatologia; Revisão; Diagnóstico.

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INTRODUCTION

Antiphospholipid syndrome (APS) is a relatively recent

autoimmune disorder defined by thrombotic events and/or obstetric morbidity in the presence of persistent elevated antiphospholipid antibodies (aPL), such as anticardiolipin antibodies (aCL), lupus anticoagulant (LA) and anti 2-glycoprotein I (aGPI). First described by Hughes et al in the early 80s there remain ongoing issues regarding nomenclature, clinical features, laboratory tests and management and much still has to be done[1-3]. Cutaneous manifestations are common and may occur as the presenting sign[4]. Although heterogeneous it is important to know which dermatological findings should prompt consideration of APS and the appropriate management of those patients, hence the unique role of dermatologists in recognizing this disease[5]. Much has been debated about when to consider APS and consensus still does not exist. However in spite of being a diagnostic challenge, physicians should be familiar with these cutaneous features since an early diagnosis is important to prevent further complications.

ANTIPHOSPHOLIPID SYNDROME

APS is traditionally referred to as primary when there is no evidence of other pathologic condition. This subgroup is thought to be slightly more prevalent[6]. Secondary APS occurs in association with other diseases, most often systemic lupus erythematosus (SLE), but also in the context of other autoimmune, malignant, drug-induced and infectious diseases[7]. Features of APS are numerous depending on the size and location of the vessels involved and are explained by vascular occlusion. Catastrophic APS occurs when acute widespread organ and tissue infarctions develop leading to multiorganic failure. It accounts for less than 1% of cases, with a mortality rate of over 50%. Cutaneous manifestations are present in up to 70 %[6,8,9].

EPIDEMIOLOGY

The real prevalence of APS is unknown[7]. Antiphospholipid antibodies can be found in 1-5% of healthy young adults. Their clinical importance in this setting is unknown but they are thought to be of low titer and transient, therefore not increasing the risk of thrombosis[10]. Primary APS is more frequent in women (2:1 to 5:1)[11]. This ratio is higher in secondary forms[6]. APS affects mostly young and middle-aged adults with 85% of patients between 15 and 50 years of age and a mean age at diagnosis of 34 years[6].

DIAGNOSIS

Clinical and laboratory criteria must be present for diagnosing APS. The broad spectrum of clinical presentations and poorly standardized laboratory tests make the diagnosis a challenge in a wide range of specialties.

Since the formulation of the Sapporo classification criteria for APS in 1999, efforts have been made to better codify the diagnosis and an update on these criteria was published in 2006[12-14]. At least one clinical criteria and one laboratory criteria must be present. According to Miyakis et al clinical criteria are: 1 - vascular thrombosis (≥1 episode of thrombosis in any tissue or organ, objectively confirmed by imaging studies or histopathology, without significant evidence of inflammation in the vessel wall); 2 - pregnancy morbidity (≥1 unexplained deaths of a normal fetus at or beyond the 10th week of gestation, or ≥1 premature births of a normal neonate before the 34th week of gestation due to eclampsia or severe pre-eclampsia or placental insufficiency, or ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation, without maternal anatomic or hormonal abnormalities and chromosomal causes excluded)[14]. Laboratory criteria rely on the presence of medium-high titers of aCL, aGPI and/or LA, on ≥2 occasions at least 12 weeks apart, detected according to international guidelines and standardized procedures[15-19]. Although the attempts for standardization, these criteria are still on debate and much has to be done to improve their reproducibility in order to avoid misclassification and overdiagnosis[20-25].

CUTANEOUS MANIFESTATIONS

Many dermatologic features have been described in association with APS. Although nonspecific and not included in the classification criteria, they are common and may be the presenting signs, providing an important clue for the diagnosis. Therefore, physicians should be familiar with the cutaneous presentations that should prompt consideration of APS. Given the lack of specificity and the similar features shared with other vascular occlusion syndromes, other causes must be excluded first. On the other hand it is important for dermatologists to be knowledgeable about APS as they can provide crucial information to uncover or confirm APS and early diagnosis will spare patients from more serious consequences of this disease.

In the first reports, dermatologic findings were found to occur in 4-55% of patients with APS[26-28]. This large variation was probably due to the lack of routine dermatologic examination[29]. The first large study related to aPL was a retrospective one involving 295 patients with circulating LA[30]. Forty-one percent had skin

lesions related to the coagulation defect as the first sign of the disease and nearly 40% of these had thrombotic events in the course of the disease, highlighting the importance of skin lesions as a marker for diagnosis and for more extensive involvement[4]. Cervera *et al.* found skin involvement in 36 of 100 patients with infection--related APS[31]. In a study of 200 patients with APS, dermatologic manifestations were noted in 49% and were the presenting sign in 30%[29]. Diógenes *et al.* reported cutaneous features as the main complaint in 40% of 39 APS patients[32].

LIVEDO

Livedo reticularis (LR) is the most frequent cutaneous manifestation of APS (Fig. 1). In spite of this strong association, the nonspecific nature should be reminded, as it occurs in a variety of physiologic and pathologic states[33]. In the aforementioned update on the classification criteria for APS it was defined as the persisting, not reversible with rewarming, violaceous, red or blue, reticular or mottled pattern of the skin[14]. It may consist of regular unbroken circles (regular LR) or irregular-broken circles (livedo racemosa). The latter is more distinctive and is considered an independent, additive thrombotic risk factor[6,29,34]. In a cohort of 1.000 European patients with APS, LR was the presenting manifestation in 20.4% and its overall prevalence was 24.1%, being higher in SLE-associated APS, in women and lower in the elderly[6]. Francès *et al.* reported similar results: LR occurred in 25.5% of patients and was the presentation sign in 17.5%[29]. In a European multicentre study, a high prevalence was also found in primary APS (24%) and SLE-related APS (20%)[27]. Another study of SLE-related APS found LR in 70% of patients, being the presenting sign in 40%[34]. The association of LR and ischemic cerebrovascular events was first described by Sneddon in 1965[35]. Sneddon s syndrome (SNS) is a rare but severe condition affecting mostly young and middle-aged women with the first cerebrovascular event occurring before 45 years of age. Livedo may precede the stroke by years. Since its description, it has been suggested that a subset of these patients have APS, predominantly manifested as cutaneous and cerebral vascular lesions[36-39]. The prevalence of aPL in SNS is variable, ranging from 40% to 50% in most series.[34,40] This relationship is not fully understood. Some believe SNS could be regarded as APS and fall into this nosological entity[41,42]. Others defend that aPL-negative and -positive patients with SNS belong to close but different subsets of this syndrome and should

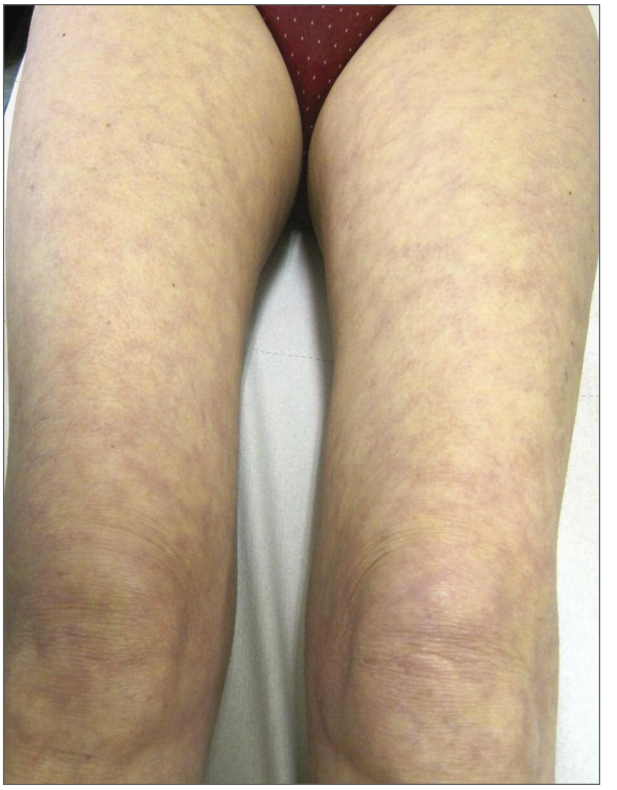

FIGURE 1. Clinical features of livedo reticularis in a patient with APS

be regarded as similar clinical expression of two distinct disorders[40,43]. Another group advocate that there is distinctive clinical, histologic and laboratory evidence to favour their separation in different disorders[44].

CUTANEOUS NECROSIS AND NECROTIC SKIN ULCERS

Cutaneous necrosis in APS is similar to that observed in other microvascular occlusion syndromes[45]. The acute onset of a retiform noninflammatory necrotizing purpura is followed by a black necrotic plaque with active purpuric borders and bullous lesions. This may remain localized or become widespread[46-51]. It is considered a major thrombotic event so long-term anticoagulation is warranted. Cervera *et al.* found cutaneous necrosis in 2.1% of patients[6]. Francès *et al.* described circumscribed cutaneous necrosis in 3.5% of patients and the extensive form in 2%[29]. Cutaneous necrosis was reported in 3% of patients with circulating LA[30].

Necrotic skin ulcers are common and may be second after livedo in frequency (Fig. 2). Cervera *et al.* observed these ulcerations as the presenting feature in

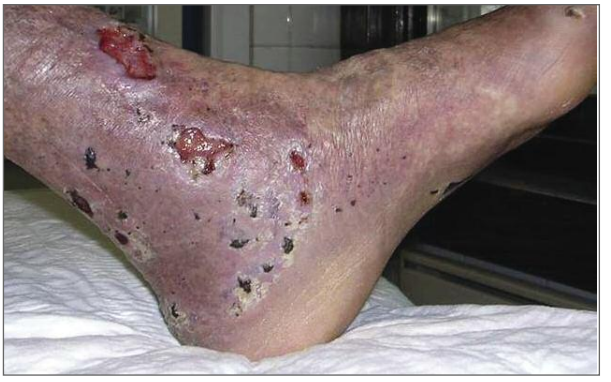

FIGURE 2. Necrotic skin ulcers on the leg of an APS patient

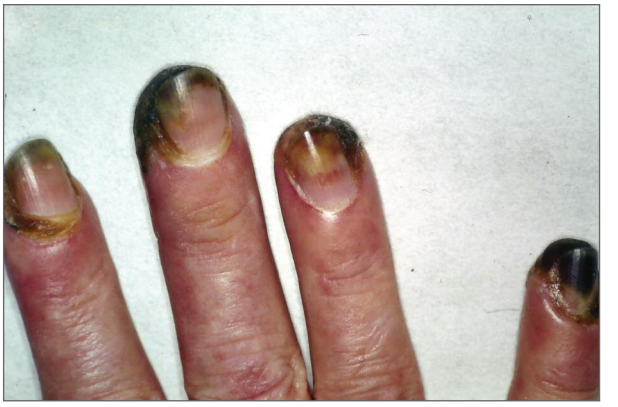

FIGURE 3. Highlight of digital gangrene on the fingers of a patient later diagnosed with APS

3.9% of 1000 APS patients with an overall prevalence of 5.5%, usually located on the extremities[6]. Francès *et al* detected necrotic skin ulcerations in 3.5% of cases, manifesting early in the disease[29]. Leg ulceration was found in 39% of patients with SLE and LA, compared to 24% of patients with SLE without LA[52]. In this case however the specific role of the aPL becomes less clear. Large ulcers resembling pyoderma gangrenosum have also been reported, though lacking the typical undermined borders and granulation tissue[4,51,53]. Recalcitrant APS-related ulcers are also not uncommon[54,55].

DIGITAL GANGRENE

Digital gangrene is a common feature among APS patients, generally preceded by digital ischemic symptoms (Fig. 3). It is a major thrombotic event sometimes leading to amputation of digits and therefore requiring full anticoagulation[29,56,57]. According to the literature, the overall prevalence ranges from 3.3% to 7.5%, manifesting as the presenting sign in 1.9-2.5% of individuals, and with no significant differences between primary and secondary forms of APS[6,26,29].

SUBUNGUAL SPLINTER HEMORRHAGES

Multiple subungual splinter hemorrhages may be a clinical feature of APS[59,60]. Usually its sudden onset is concurrent with other thrombotic events leading to a probable underestimation of this condition, as shown by the low prevalence reported in most series, ranging from 0.7% to 5%[6,29].

PSEUDOVASCULITIC LESIONS

Pseudovasculitic lesions require a high index of suspicion. They mimic cutaneous vasculitis and may be misdiagnosed if a biopsy is not performed, leading to incorrect management and exposure to potentially deleterious treatments[61,62]. Many features are described, including purpura (Fig. 4), ecchymoses, red macules, small erythematous or cyanotic lesions on hands and feet (Fig. 5), painful papules or nodules on the limbs, ears, neck or thighs and localized necrotic areas of the neck and anterior chest[47,63-66]. These lesions are found in 2-2.6% of patients as the first sign of the disease and appear during its course in 3-3.9% of patients[6,29]. Ecchymoses and purpura were detected in 14% of patients with LA[30].

LIVEDOID VASCULOPATHY AND ATROPHIE BLANCHE

Livedoid vasculopathy, otherwise known as livedoid vasculitis, segmental hyalinizing vasculitis or livedo reticularis with summer/winter ulceration, was originally described in 1967[67]. It mostly affects young to middle-aged women and consists in focal purpuric painful lesions, usually on the legs and feet, that break down to form irregularly shaped ulcers. These heal slowly, leaving porcelain-white, stellate, atrophic scars surrounded by telangiectasia, haemosiderin deposition and hyperpigmentation, the so-called atrophie blanche[68]. The pathogenesis of this condition is not fully understood but the histology shows a thrombotic process rather than vasculitis, hence the preferred term "vasculopathy"[69,70]. It has been described as a sole entity and in association with other conditions, including APS. There are no large series documenting the prevalence of this finding but the association with APS has been well documented, thus allowing it into the cutaneous manifestations of this syndrome[4,68,71-73].

DEGOS'-LIKE LESIONS

Degos disease, also known as malignant atrophic

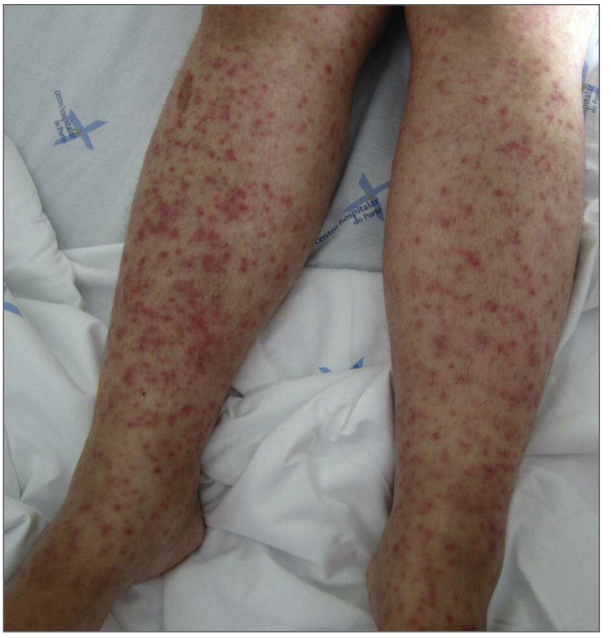

FIGURE 4. Cutaneous lesions on the legs clinically mimicking vasculitis – pseudovasculitc lesions on a female patient with APS

papulosis, is a rare multisystem vasoocclusive disorder affecting the skin, gastrointestinal tract and central nervous system. Skin lesions consist in crops of small painless yellowish papules over the trunk and extremities that develop a central depression and later a porcelain-white scar. It was first described in association with aPL by Engler *et al.* in 1984[74]. This was not confirmed later by Assier et al who speculated that the patients with apparent Degos disease had instead atrophie blanche lesions resembling those of Degos[75]. It is suggested that patients with the benign form of this disease (limited to the skin) are more prone to have aPL[73]. There are no data in the literature regarding the prevalence of this feature in APS nor of the prevalence of aPL in patients with Degos' disease.

PRIMARY ANETODERMA

Primary anetoderma is a rare disorder characterized by circumscribed depressions or patches of slack skin with an atrophied appearance (Fig. 6). Since its first description in association with APS in the early 90s, anetoderma has repeatedly been reported as an APS-related feature[76-81]. It is thought to be an important skin sign for autoimmune disorders, including APS[82]. So far, in patients with SLE these lesions were always associated with aPL, being identified in 15% of these patients with LA but in none of the group where LA was absent[52,82].

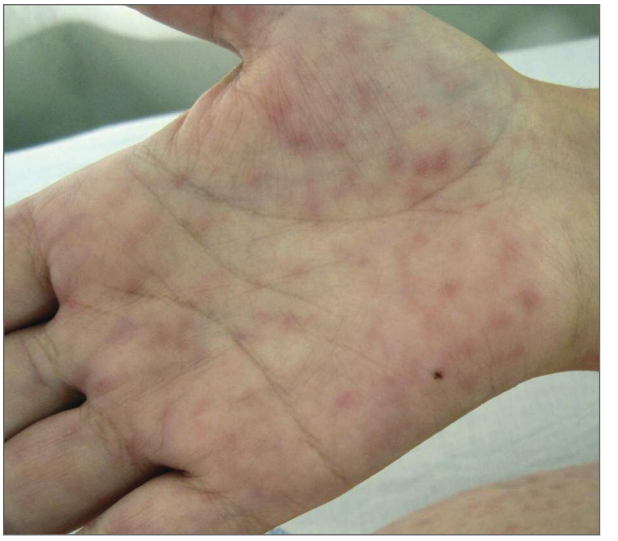

FIGURE 5. Erythematous macules on the hands of a patient with APS

HISTOPATHOLOGY OF THE CUTANEOUS LESIONS

Although the heterogeneity of the aforementioned cutaneous findings, most of them have in common an important histopathologic feature: noninflammatory thrombosis of the dermal vessels[4,29,32,73]. True vasculitis is not a feature. Early lesions usually show dermal edema, hemorrhage and occasional epidermal necrosis. Late-stage lesions may show reactive capillary proliferation, hemosiderin deposition and epidermal atrophy[45,83-86]. Reactive angioendotheliomatosis has also been reported[87,88]. Although nonspecific this is typical, highlighting the importance of a skin biopsy in many circumstances, especially when there s the need to exclude other conditions in order to select appropriate treatment. In the particular case of anetoderma, histopathologic examination shows elastic fibers depletion in the dermis under special stains, usually Verhoeff-van Gieson elastin stain[28,73].

MANAGEMENT OF CUTANEOUS MANIFESTATIONS

Diagnosing APS is not easy, particularly when we are dealing with cutaneous manifestations. When facing a patient with skin lesions suggestive of APS it s important to keep in mind that they re not included in the classification criteria. In fact, much has been debated when it comes to this fact. In the consensus statement a special consideration was given to LR, undoubtedly frequent but not specific[14]. The committee considered

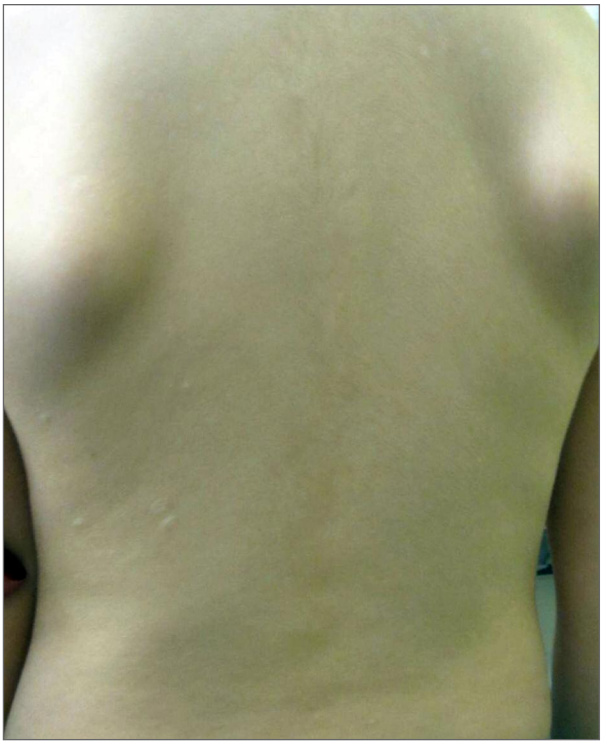

FIGURE 6. Clinical features of anetoderma, with localized patches of slack skin with an atrophied appearance

that inclusion of LR as independent clinical criterion for definite APS would decrease diagnostic specificity, even though its association with APS is recognized. Other skin manifestations of APS are considered rare and none merits inclusion as a criterion. Another problem is how to classify cases with aPL and non-criteria clinical manifestations of APS, a common situation for dermatologists. "Probable APS", "features associated with APS" or "non-criteria features of APS" are reasonable terms[14]. With these limitations in mind, one should know that although suggestive of the diagnosis of APS, a patient manifesting skin lesions consistent with the diagnosis and with serological evidence of circulating aPL still must meet additional clinical criteria. Such a patient can be classified as having probable APS but a definite diagnosis cannot be made[89]. Recognizing the appropriateness of searching for aPL is another important issue since generalized searches are highly discouraged in order to avoid overdiagnosis and overtreatment. Testing should be limited to patients who have a significant probability of having APS[20]. Diagnosis is more likely in a young patient, without other risk factors for thrombosis, presenting with an unexplained cutaneous lesion that appears to be secondary to thrombosis or vascular occlusion. A skin biopsy is helpful when it is necessary to document vascular occlusion or exclude other conditions. In the absence of thrombosis APS cannot be diagnosed. When thrombosis is documented the presence of aPL make the diagnosis: if present the patient has APS, if absent only probable-APS can be assumed.

TREATMENT

Anticoagulation is the mainstay of the management of APS. In order to provide optimal care this should be individualized according to patient s clinical status and history of thrombotic events. The standard therapy is intravenous or subcutaneous heparin followed by warfarin. During pregnancy, low molecular weight heparin and aspirin should be used. In general, patients with the first venous thrombosis should have an INR of 2.0-3.0 and patients with arterial thrombosis or recurrent events should have an INR of > 3,0[90-93]. Additional vascular and thrombotic risk factors should be actively reduced. Treatment of catastrophic APS, although unsatisfactory, usually comprises combination therapy with high dose intravenous steroids and anticoagulation, intravenous gammaglobulin and repeated plasma exchanges[8,9,90-93]. Duration and intensity of therapy remain controversial, so further trials are required to establish the optimal management of APS patients. In the meantime anticoagulation drugs are usually prescribed for life. Asymptomatic patients with circulating aPL or patients who do not display the formal classification criteria are usually treated with low dose aspirin or clopidogrel, although no evidence-based recommendations have been provided supporting this attitude. The same is also true for statins, antimalarials (especially in SLE) and angiotensin-converting enzyme inhibitors, recently suggested for prophylactic treatment[94-97]. In what concerns the treatment of patients with skin lesions, both dermatologic manifestations and the overall clinical situation should be considered. In the absence of randomized control trials, therapy for dermatologic manifestations remains empirical and no treatment has been systematically effective. Widespread cutaneous necrosis and digital gangrene are considered major thrombotic events requiring long-term anticoagulation treatment. If even so lesions continue to spread, plasma exchange, steroids and/or cytotoxic agents have been reported to

be successful[29,48,49,73,98,99]. For other isolated skin presentations, combination therapy with aspirin and dipyridamol or pentoxifylline has been effective in some cases, but the potential benefit of this association still needs to be determined[29,73,94-97]. Anyway, cutaneous lesions frequently recur or extend and in those circumstances anticoagulation is usually prescribed. When all of these fail, treatment may be very difficult and many alternatives have been proposed in the literature, with variable response, namely cyclophosphamide, azathioprine, rituximab, intravenous gamma globulins, fibrinolytic agents, sildenafil, androgenic anabolic steroids and autologous skin grafting[29,54,55,73,98-100].

CONCLUSION

Many cutaneous presentations have been described in association with APS. Although nonspecific and not included in the classification criteria, dermatologic findings are frequent and may be the presenting feature making them an important clue in the diagnosis of this disease. For that reason, it is important to be familiar with these cutaneous features and to recognize when APS investigation should be pursued. Being knowledgeable about APS, physicians can provide crucial information to uncover or confirm APS and early diagnosis will spare patients from more serious consequences of this disease.

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