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Cutaneous Manifestations of Antiphospholipid Syndrome: A Scoping Review

Fatema Khaled Alhammadi[*1], Sara Khaled Alhammadi[2]

[*1]Internal Medicine Specialist, Saudi Board of Internal Medicine, MRCP (UK)

[2]Dermatologist and Aesthetic Medicine Specialist, Egyptian Fellowship of Dermatology, American Board of Aesthetic Medicine. Email: sara.abubakr287@gmail.com

***Corresponding author:**

Fatema Khaled Alhammadi,

Email ID: Fatema.khaled@hotmail.com

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ABSTRACT

Background: Antiphospholipid Syndrome (APS) is a systemic autoimmune disorder characterized by vascular thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies. While its hematological and obstetric manifestations are well established, cutaneous manifestations are frequently overlooked despite their diagnostic and prognostic significance. The skin often provides early clinical clues that may precede systemic events, emphasizing the need for greater clinical awareness.

Objective: This scoping review aims to explore, map, and synthesize existing literature on the spectrum of cutaneous manifestations associated with APS, elucidating their clinical presentations, diagnostic relevance, and implications for patient care.

Methods: A systematic search was conducted across PubMed, Scopus, Web of Science, and Google Scholar databases, supplemented by manual screening of references. Studies were eligible if they discussed skin-related features in APS, were published in English, involved human participants, and provided primary or secondary data on dermatological findings. After duplicate removal and eligibility screening, 5 articles were selected from an initial pool of 354 studies. Reasons for exclusion included irrelevance to cutaneous features, non-availability of full texts, language barriers, or being non-peer-reviewed formats.

Results: The review identified a range of cutaneous manifestations associated with APS, including but not limited to livedo reticularis, digital gangrene, skin ulcers, purpura, and necrotic lesions. Livedo reticularis emerged as the most commonly reported skin manifestation, often presenting as a chronic, non-inflammatory vascular pattern. In several cases, cutaneous signs were the initial clinical features that led to further diagnostic investigation for APS. The dermatologic findings were noted to correlate with both thrombotic risk and systemic involvement, particularly in cases of catastrophic APS (CAPS).

Conclusion: Cutaneous manifestations play a critical role in the early detection and comprehensive management of APS. Recognizing these signs can aid clinicians in timely diagnosis, especially in patients without overt thrombotic or obstetric symptoms. Further research with standardized reporting and prospective designs is needed to strengthen clinical understanding of these manifestations and their prognostic implications.

Keywords: *Antiphospholipid Syndrome, APS, cutaneous manifestations, livedo reticularis, skin lesions, autoimmune disease, catastrophic APS, dermatologic signs*

1. INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder defined by the persistent presence of antiphospholipid antibodies (aPL) and characterized clinically by recurrent arterial or venous thromboses and/or obstetric complications such as recurrent miscarriages, stillbirth, or severe preeclampsia. First described in 1983 by Hughes, APS is now recognized as a major cause of acquired thrombophilia, significantly contributing to morbidity and mortality among affected individuals (Hughes, 1983; Miyakis et al., 2006).

Cutaneous manifestations of APS are among the earliest and most visible signs of the syndrome, often preceding life-threatening thrombotic events. The skin is a critical site for identifying the underlying vascular pathology, as it is susceptible to both macrovascular and microvascular complications stemming from aPL-mediated endothelial dysfunction and prothrombotic states. These dermatologic findings, which range from livedo reticularis and ulcers to digital gangrene and purpura, serve not only as diagnostic clues but also as markers of disease severity and systemic involvement (Cervera et al., 2009).

Despite their diagnostic and prognostic significance, cutaneous manifestations are frequently under-recognized or misattributed to other conditions. Their polymorphic presentation and overlap with other autoimmune and vasculopathic disorders demand a high index of suspicion, especially in young individuals with unexplained thrombotic events or recurrent pregnancy losses. Moreover, skin lesions in APS may represent a heralding sign of catastrophic antiphospholipid syndrome (CAPS), a fulminant variant associated with multi-organ failure and high mortality (Asherson et al., 1992).

The classification criteria for APS, revised by an international consensus in 2006, emphasize the role of laboratory confirmation of aPL antibodies—including lupus anticoagulant, anticardiolipin antibodies, and anti-β2 glycoprotein I antibodies—present on two or more occasions at least 12 weeks apart (Miyakis et al., 2006). However, many patients with significant clinical disease, including cutaneous involvement, may not fulfill the strict criteria, highlighting the importance of integrating clinical judgment and dermatologic findings in diagnosis.

Given the heterogeneity of skin presentations and their potential systemic implications, a multidisciplinary approach is essential for effective management. Dermatologists play a pivotal role in early recognition and diagnosis, while rheumatologists, hematologists, and obstetricians contribute to comprehensive patient care. Treatment strategies focus primarily on anticoagulation, but immunomodulation may be warranted in cases with prominent inflammatory or ulcerative skin disease (Ruiz-Irastorza et al., 2010).

This review aims to provide an updated and thorough overview of the cutaneous manifestations of APS, elucidating their pathophysiological underpinnings, clinical features, diagnostic relevance, and therapeutic approaches. By raising awareness of these dermatologic signs, clinicians can improve early detection and management, potentially averting severe systemic complications.

2. METHODS

Search Strategy and Data Sources

A comprehensive literature search was conducted across multiple academic databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify studies examining the cutaneous manifestations of Antiphospholipid Syndrome (APS). The search included articles published up to February 2025. Keywords used included combinations of: "Antiphospholipid Syndrome," "cutaneous manifestations," "skin lesions," "dermatologic findings," "livedo reticularis," "digital gangrene," "skin ulcers," and "catastrophic APS." Boolean operators (AND, OR) and Medical Subject Headings (MeSH) were utilized to refine the search.

Eligibility Criteria

Inclusion Criteria

Studies were deemed eligible for inclusion if they met several key criteria. Eligible studies focused explicitly or substantially on the cutaneous manifestations of antiphospholipid syndrome (APS), offering relevant insights into skin involvement associated with the condition. Both primary research—such as case series, cohort studies, and cross-sectional studies—and secondary research, including systematic or narrative reviews, were considered, provided they addressed dermatological aspects of APS. Additional eligibility requirements included publication in peer-reviewed journals, availability in the English language, involvement of human participants, and the inclusion of sufficient detail regarding dermatological findings such as livedo reticularis, ulcers, gangrene, and purpura.

Exclusion Criteria

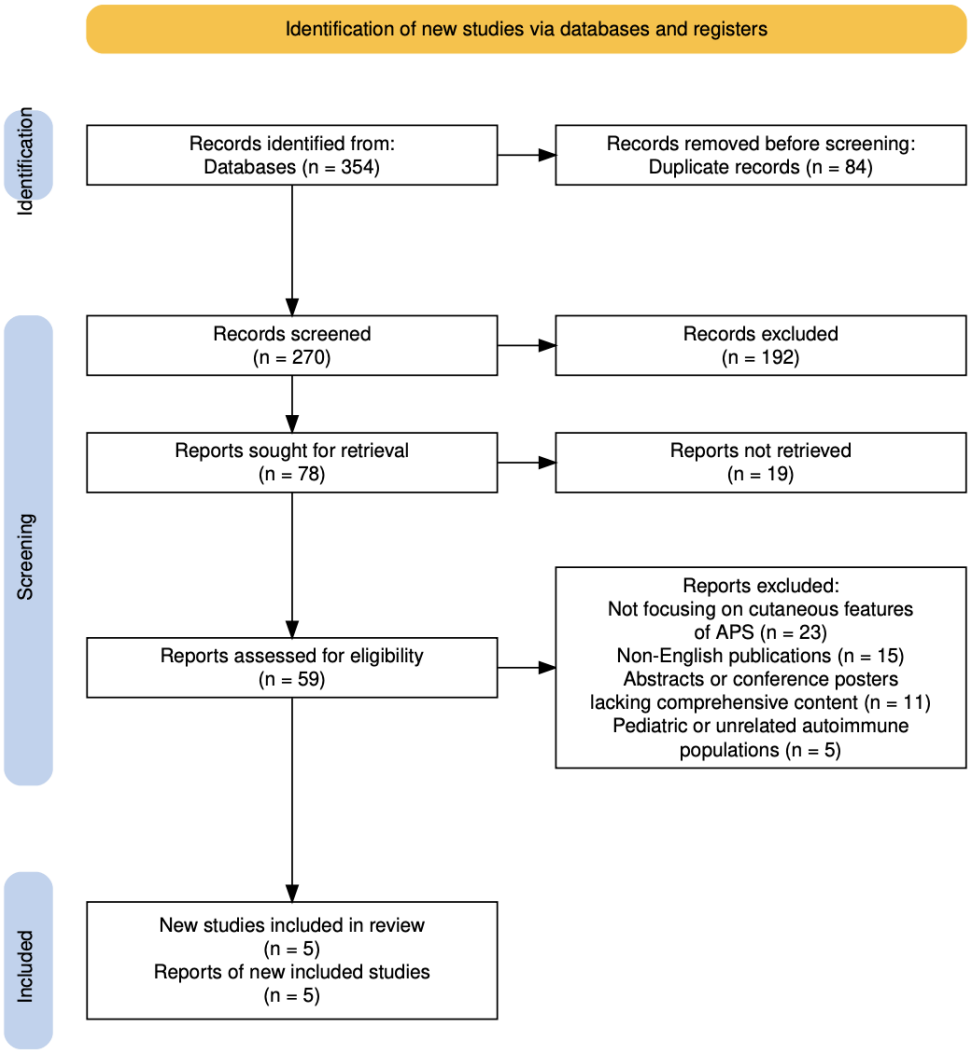
Articles were excluded based on several predefined criteria to ensure the relevance and quality of the final selection. Duplicate entries found across databases and repositories were removed during the initial screening phase. Articles with inaccessible full text, including those not retrievable via institutional access or interlibrary loan, were excluded. Studies that did not focus on or lacked sufficient detail regarding the cutaneous features of antiphospholipid syndrome (APS) were also excluded. Additional exclusions included non-English publications, as well as abstracts, conference proceedings, editorials, or opinion pieces that did not contain primary data or substantive review content. Furthermore, studies centered on other autoimmune conditions without direct relevance to APS-specific dermatologic findings, as well as animal or in vitro studies, were not considered for inclusion.

Screening and Selection Process

An initial total of 354 articles were retrieved through the combined search strategy. After the removal of 84 duplicate records,

270 articles remained for title and abstract screening. This phase was conducted independently by two reviewers, with any discrepancies resolved through discussion and consensus. Subsequently, 78 full-text articles were assessed for eligibility. During this stage, 23 articles were excluded for not focusing on the cutaneous features of antiphospholipid syndrome (APS), 19 were excluded due to the unavailability of full text, 15 were discarded for being non-English publications, 11 were excluded as they were abstracts or conference posters lacking comprehensive content, and 5 were removed due to their focus on pediatric or unrelated autoimmune populations. After rigorous filtering based on the predefined inclusion criteria, 5 articles were included in the final synthesis. The screening and selection process was documented using a PRISMA-style flow diagram.

Figure 1. PRISMA Flow Diagram for Study Selection: Cutaneous Features of APS



Data Extraction and Synthesis

Data from the included studies were extracted using a standardized form designed to capture key study details, including author(s) and publication year, study design and setting, population characteristics, the type and frequency of reported cutaneous manifestations, and their diagnostic implications or relevance to APS classification and management. Due to the heterogeneity in study designs and data types—ranging from narrative reviews and cohort studies to case-based reviews—a narrative synthesis approach was adopted. The findings were thematically grouped based on the type of skin lesion, such as livedo reticularis, ulcers, and necrosis, along with their frequency, diagnostic significance, and implications for clinical practice.

3. RESULTS

Study Selection

Five studies met the inclusion criteria and were included in this scoping review. The selected literature comprised a mix of study designs: two narrative reviews, one systematic review, one cross-sectional population study, and one case report. All

articles provided focused insights or clinical data regarding cutaneous manifestations associated with Antiphospholipid Syndrome (APS), either as primary symptoms or within the context of broader APS-related investigations. Figure 1 summarizes the study selection process.

Study Characteristics

The included studies were published between 2006 and 2024 and represented diverse geographic and clinical settings, including population-level analyses (Rezaei et al., 2024), dermatologic case series (Caporuscio et al., 2015), and broad narrative syntheses (Pires-da-Rosa et al., 2021; Pinto-Almeida et al., 2013). The study by Lim et al. (2006) focused on therapeutic outcomes but also addressed skin findings in the context of treatment strategies. A detailed summary of each article is provided in Table 1.

Synthesis of Results

Cutaneous Manifestations Identified

The most commonly reported cutaneous features in antiphospholipid syndrome (APS) across the included studies encompassed a spectrum of dermatologic manifestations, with livedo reticularis (LR) and livedo racemosa (LRa) being the most frequently cited. LR was consistently described as an early and often presenting sign of APS, with prevalence estimates ranging from 20% to 70%, depending on the cohort and diagnostic criteria employed. LRa, in particular, was noted for its association with arterial thrombotic events and was even considered an independent thrombotic risk factor in some studies (Pinto-Almeida et al., 2013; Pires-da-Rosa et al., 2021).

Cutaneous necrosis and ulcers were also prominent, especially in cases of severe or catastrophic APS. These manifestations, typically involving the lower limbs, were indicative of dermal small vessel thrombosis. For example, Caporuscio et al. (2015) reported a case in which widespread necrotic bullous lesions served as the initial clinical sign of APS, highlighting their potential diagnostic significance.

Digital gangrene and purpura, though less common, were recognized as severe cutaneous indicators suggestive of systemic involvement and advanced thrombotic disease. Pinto-Almeida et al. reported prevalence estimates between 3.3% and 7.5% for these findings, underscoring their clinical relevance given the associated risks of amputation and systemic complications.

Superficial thrombophlebitis and chronic ulceration were also documented, particularly in both primary and secondary APS cases involving comorbid autoimmune conditions such as systemic lupus erythematosus. These findings were frequently noted in narrative reviews and historical clinical series, reflecting their persistent relevance in clinical assessment.

Lastly, a range of non-specific dermatologic findings was reported, including Raynaud's phenomenon, urticaria-like vasculitis, subungual splinter hemorrhages, and erythematous nodules. While these features appeared less frequently in the literature, their occurrence alongside serologic positivity for antiphospholipid antibodies suggests potential diagnostic value and warrants further clinical attention.

Non-Criteria Manifestations and Classification Challenges

The review by Pires-da-Rosa et al. (2021) emphasized that many cutaneous manifestations, although clinically significant, remain outside of current APS classification criteria. The authors advocated for the inclusion of dermatologic signs—especially livedo patterns, ulcers, and vasculopathic lesions—in future revisions of APS diagnostic frameworks.

Similarly, Pinto-Almeida et al. (2013) detailed that up to 70% of patients with APS may present initially with cutaneous signs, underscoring the potential of dermatologic findings as sentinel indicators. These reviews highlighted the need for increased clinical awareness, especially among dermatologists and rheumatologists.

Thrombotic Risk and Dermatologic Clues

The case report by Caporuscio et al. (2015) uniquely illustrated the co-occurrence of APS and protein S deficiency in a patient presenting with necrotizing skin lesions, demonstrating the interplay between inherited and acquired thrombotic risk factors. Histologic examination confirmed dermal vascular thrombosis, supporting a definitive APS diagnosis.

The systematic review by Lim et al. (2006), while primarily focused on anticoagulation regimens, indirectly supports the inclusion of dermatologic symptoms as early warning signs that may guide timely initiation of therapy and prevent systemic thrombotic events.

Epidemiologic and Population-Level Insights

Rezaei et al. (2024) utilized NHANES data to explore dermatologic conditions among veterans, revealing significantly higher odds of skin cancer, melanoma, and psoriasis. Although APS was not the central focus, their work contributes to the broader understanding of autoimmune-related cutaneous presentations and supports the relevance of dermatologic screening in at-risk populations.

Table 1. Characteristics of Included Studies

Author (Year)	Study Design	Population/Setting	Focus	Key Cutaneous Findings	Statistical Significance	Confounders Controlled	Limitations	Relevance to APS
Rezaei et al. (2024)	Cross-sectional (NHANES)	61,307 adults (6,753 veterans) in US	Compare skin conditions in veterans vs. nonveterans	↑ Skin cancer (9.0% vs 2.9%), melanoma (2.2% vs 0.6%), psoriasis (4.5% vs 2.9%)	ORs: Skin CA 1.72, Melanoma 2.27, Psoriasis 1.61; all $p < 0.01$	Age, sex, race, income, smoking, insurance, access to care	Self-reported data, no clinical validation, cross-sectional	APS has skin signs; understanding risk patterns aids differential diagnosis and monitoring
Pires-da-Rosa et al. (2021)	Review Article	Literature Review	Overview of non-criteria manifestations in APS	Livedo reticularis/racemosa, livedoid vasculopathy, skin ulcers	Not applicable	Not applicable	Potential publication bias; variability in study designs and definitions across reviewed studies	Highlights importance of recognizing dermatological signs not included in APS classification criteria
Lim et al. (2006)	Systematic Review	Various studies	Treatment of thrombosis risk in patients with APS	Moderate-intensity warfarin (INR 2.0-3.0) reduces recurrent venous thrombosis risk by 80%-90%; no added benefit from high-intensity warfarin (INR >3.0); aspirin and moderate-intensity warfarin are equally effective for preventing recurrent stroke in patients with prior stroke and a single	Varies across studies	Varies across studies	Limited randomized trials; heterogeneity in study designs; potential publication bias; applicability to diverse populations may be limited.	Provides evidence-based guidance on anticoagulation strategies for preventing thrombotic events in APS patients.

				positive antiphospholipid antibody test.				
Caporuscio et al. (2015)	Case Report	44-year-old male patient in Italy	Atypical cutaneous manifestations as the initial sign of APS	Describes a patient with bullous, necrotic skin lesions due to APS and protein S deficiency; histology showed necrotising vasculitis with dermal thrombosis. Treatment with corticosteroids, azathioprine, and aspirin led to remission.	Not applicable (descriptive case)	None explicitly controlled	Single patient case; no generalizability; observational bias	Emphasizes skin lesions as potential first sign of APS; highlights need for early recognition and comprehensive workup.
Pinto-Almeida et al. (2013)	Literature Review	Review of existing literature (various settings, international data)	Clinical features, diagnosis, and management of cutaneous manifestations of APS	Cutaneous signs can be the first manifestation of APS in up to 70% of patients. Livedo reticularis is most frequent; others include necrosis, ulcers, digital gangrene. Management involves anticoagulation, immunosuppression, and dermatologic care. Highlights diagnostic challenges and	Summarizes prior studies with statistical data	Not applicable in review format	Data heterogeneity, inconsistent diagnostic criteria, non-inclusion of rare lesions in classification schemes	Provides broad understanding of cutaneous signs that may signal APS; stresses early diagnosis to avoid severe outcomes.

				variability of dermatologic signs.				

4. DISCUSSION

Cutaneous manifestations represent an important, and often under-recognized, facet of antiphospholipid syndrome (APS), serving as potential early indicators of systemic disease and aiding in timely diagnosis and management. The skin, with its easily visible vasculature and sensitivity to microcirculatory changes, often reflects the thrombotic and inflammatory pathophysiological processes characteristic of APS (Tektonidou, 2005). In some cases, dermatologic signs precede major thrombotic events, offering a critical window for early intervention (Asherson et al., 1992).

Livedo reticularis (LR) is the most frequently reported cutaneous finding in APS and is regarded as a hallmark lesion, especially in primary APS. Its presence is associated with higher thrombotic burden and increased risk of arterial events such as stroke (Cervera et al., 2002; Rodriguez-Pintó et al., 2016). LR likely results from occlusion or constriction of dermal vessels by thrombi, leading to a reticulated, violaceous skin pattern. Importantly, when LR becomes fixed and persistent (livedo racemosa), it often correlates with more severe systemic involvement and may warrant investigation for catastrophic APS (CAPS) (Asherson et al., 1992).

Other ischemic lesions such as digital gangrene, acral necrosis, and skin ulcers are manifestations of small-vessel thrombosis, and while less common than LR, they typically indicate more severe disease. Their presence often necessitates urgent evaluation and aggressive anticoagulation to prevent progression to life-threatening complications (Cervera et al., 2009). Subungual splinter hemorrhages, though non-specific, may similarly reflect ongoing microvascular involvement and should prompt further systemic assessment when found in the appropriate clinical context (Alarcón-Segovia et al., 1984).

Inflammatory skin lesions, including cutaneous vasculitis, urticaria-like eruptions, and purpura, have also been documented. While less specific to APS, these findings may overlap with coexisting autoimmune conditions such as systemic lupus erythematosus (SLE), which commonly accompanies secondary APS. The presence of such lesions underscores the importance of a multidisciplinary approach in diagnosis and management, particularly in cases where skin findings are the initial presenting symptom (Ruiz-Irastorza et al., 2010).

The association between skin findings and neurological complications in APS is particularly interesting. For instance, the coexistence of livedo racemosa with cerebrovascular events has been described as a key feature of Sneddon syndrome, a condition strongly associated with aPL antibodies (Roldan et al., 2006). This highlights the diagnostic value of integrating dermatologic and neurologic findings in suspected APS cases.

Histopathological examination of APS-related skin lesions often reveals thrombosis without vasculitis, supporting the concept of a primary thrombotic vasculopathy rather than an inflammatory process. However, in some cases, mild perivascular lymphocytic infiltrates or true leukocytoclastic vasculitis may be observed, particularly when immune complexes contribute to endothelial injury (Asherson et al., 1992; Cervera et al., 2009).

From a management standpoint, anticoagulation remains the cornerstone of therapy for cutaneous and systemic manifestations of APS. Long-term use of warfarin or direct oral anticoagulants (DOACs) may reduce the risk of recurrence, although the efficacy of DOACs in APS remains debated and is currently not recommended in high-risk patients (Pengo et al., 2018). In cases of ulcerative or necrotic lesions, adjunctive therapies such as corticosteroids, intravenous immunoglobulin (IVIG), or plasma exchange may be considered, especially when CAPS or associated autoimmune disorders are present (Tektonidou, 2005).

Despite increasing recognition, significant knowledge gaps persist. There is a need for standardized definitions and classification of cutaneous APS lesions, as well as for prospective studies to evaluate their predictive value and response to therapy. Furthermore, the lack of specific diagnostic criteria for cutaneous APS underscores the importance of clinical vigilance and multidisciplinary collaboration.

5. CONCLUSION

Cutaneous manifestations, particularly livedo reticularis, ulcers, and digital gangrene, are common and clinically significant features of Antiphospholipid Syndrome (APS). These dermatologic signs often precede or accompany thrombotic events and may serve as early indicators of underlying disease. Despite their diagnostic relevance, they remain underrepresented in current classification criteria. This review underscores the need for increased clinical recognition and suggests that integrating cutaneous features into future APS diagnostic frameworks could enhance early detection and patient management.

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