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Acrocyanosis: primary or secondary form? An observational study

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Abstract

Introduction: Acrocyanosis is the most common form of angiodystonic vascular acrosyndrome, characterized by functional microcirculatory alterations without structural vessel damage. It is traditionally classified as either primary or secondary, the latter often associated with underlying conditions.
Methods: Some observations suggest a frequent association between acrocyanosis and connective tissue diseases (CTDs). To investigate this, we conducted a study on 53 patients diagnosed with acrocyanosis: 45 females and eight males, 15 to 82 years old, with a mean age of 35 years. Secondary acrocyanosis was identified in 24 patients (45.3%).
Results: Advanced age (≥ 40 years) was a significant risk factor for secondary acrocyanosis (relative risk = 2.5, 95% confidence interval: 1.4–4.5, $p = 0.002$). No significant differences were observed between sexes. CTDs were the most common conditions associated with acrocyanosis (32% of the study population and 71% of the secondary forms).
Conclusions: Although generally considered benign, acrocyanosis may indicate an underlying systemic disease. Clinical examination remains essential for the diagnosis of acrocyanosis. Our findings reveal a high prevalence of secondary acrocyanosis associated with CTDs. Patients with strong clinical suspicion should be referred to specialized centers for capillaroscopy and antinuclear antibody testing.

Keywords: acrocyanosis, capillaroscopy, connective tissue diseases, microcirculation, non-invasive diagnosis

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Introduction

Acrocyanosis is one of the most significant forms of angiodystonic vascular acrosyndrome (AVA), characterized by functional alterations in peripheral microcirculation without structural vessel damage (1). Clinically, it presents as cold extremities and persistent, painless cyanosis (rather than paroxysmal episodes). It is the most frequent form of AVA (2).

Acrocyanosis is traditionally classified as primary or secondary. Primary acrocyanosis typically follows a benign course and may improve over time. However, it may worsen, particularly with cold exposure, potentially leading to acute pernio (chilblains).

Secondary acrocyanosis (sometimes referred to as pseudo-acrocyanosis) includes peripheral cyanoses caused by other underlying conditions. These can be divided into two categories (3, 4). The first category, regional and typically unilateral conditions, include slowing of venous flow (e.g., post-thrombotic syndrome, pressure-induced venous stasis, or impaired or inadequate deambulation), neurogenic peripheral vascular dysregulation (e.g., poliomyelitis, ictus, or medullary lesions), arterial hypoperfusion (e.g., thromboangiitis obliterans or Buerger's disease). The second category, systemic and typically bilateral conditions, are due to cardiogenic factors (e.g., heart and/or respiratory failure, or cardiovascular diseases associated with cyanosis), hematologic conditions (e.g., polycythemia and other myeloproliferative disorders, or cryoglobulinemia), neoplasms, drug-induced conditions, infectious diseases, psychiatric disorders, or eating disorders (e.g., anorexia nervosa or chronic fasting).

Of particular interest are secondary forms associated with connective tissue diseases (CTDs). These forms often present bilaterally and may follow an insidious course, especially in young individuals or when other symptoms suggestive of an underlying CTD are absent. As a result, they can be misclassified as primary acrocyanosis. However, recent data on the true incidence of secondary acrocyanosis, especially in the context of CTDs, remain limited in the literature.

This study investigates the prevalence of secondary acrocyanosis among patients initially diagnosed with primary acrocyanosis and explores its potential association with underlying CTDs. We hypothesize that a proportion of cases currently labeled as primary acrocyanosis are, in fact, secondary forms related to undiagnosed CTDs. To address this hypothesis, we analyzed a cohort of patients referred to our center with a diagnosis of primary acrocyanosis.

Methods

This prospective observational study was conducted between January 2018 and January 2020 at three specialized secondary care centers for vascular medicine. As a cross-sectional study, no follow-up period was included.

A total of 53 patients (45 females and eight males, mean age 35 years, age range 15–82) were recruited based on predefined inclusion criteria. Given the exploratory nature of the study, the sample size was determined by the availability of eligible patients rather than a formal power calculation. Patients were referred by general practitioners, internists, rheumatologists, and dermatologists, and some also self-referred to the clinic.

Participants were selected based on the presence of acrocyanosis (purplish cyanosis and cutaneous hypothermia of the hands) for at least 2 months. Exclusion criteria were: 1) current or prior diagnosis of CTD; 2) presence of Raynaud's phenomenon, which suggests a possible CTD and independently warrants capillaroscopic and serological evaluation; 3) ongoing vasoactive therapy

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(e.g., vasodilators), which may alter acrocyanosis presentation, potentially leading to a distorted diagnosis (beta-blocker use was permitted because it can induce or reveal secondary acrocyanosis); and 4) known diagnosis of neoplasia.

None of the participants used tobacco, cannabis, or alpha-agonist drugs. Matching was not applied due to the absence of a case-control design. All eligible patients consented to participate; no exclusions or non-participation occurred, and therefore a flow diagram was not included. Written informed consent was obtained, with parental consent for minors.

Each patient underwent standardized evaluations to identify secondary acrocyanosis:

1. A comprehensive medical history (anamnesis) was taken to document symptoms, medical history, and any risk factors.
2. A clinical and instrumental examination (color Doppler ultrasonography) was performed, including skin examination, systematic clinical examination of the organs, and examination of the peripheral vascular system.
3. Nailfold videocapillaroscopy was conducted to examine capillary beds. Capillaroscopy was classified as pathological if at least one of the following criteria was met:
   a. Presence of megacapillaries (abnormally large capillaries);
   b. Capillary count less than eight per mm of linear distance;
   c. At least three quantitative or qualitative anomalies (on a single finger or multiple fingers) among the following (5):
      i. Angiotectonic disorder (spatial alterations of the capillary loops and network);
      ii. Non-homogeneous loop morphology;
      iii. Avascular areas;
      iv. Pseudo-avascular areas;
      v. Ectasias (30–50 microns).
4. Hematochemical tests included the following: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC), protein electrophoresis, antinuclear antibodies-extractable nuclear antigens (ANA-ENA) test, rheumatoid factor, cryoglobulin test, complement test, and antiphospholipid antibodies (APLA).

Patients with alterations or abnormal findings on clinical, capillaroscopic, or laboratory evaluation were referred to a specialized rheumatology center or other relevant facilities for further assessment. Consecutive patient recruitment minimized selection bias, and standardized diagnostic criteria and independent specialist confirmation reduced misclassification. Preliminary investigations and laboratory tests were repeated for further verification, and additional tests recommended by the specialist team were performed to establish a definitive diagnosis.

Secondary acrocyanosis was confirmed according to international guideline criteria by the relevant specialist teams at the reference centers for each pathology.

Statistical analysis

Statistical analyses were conducted to determine the proportion of patients diagnosed with secondary acrocyanosis and to identify potential risk factors. Data were analyzed according to the classification of acrocyanosis (primary vs. secondary), with comparisons based on age and sex. All variables were fully available for statistical analysis. No data were missing for key outcome variables.

Based on prior literature and observed prevalence patterns in secondary acrocyanosis, age was analyzed as a categorical variable (< 40 or ≥ 40 years). No other continuous variables were categorized.

Univariate logistic regression was used to assess factors associated with the outcome of secondary acrocyanosis. Multivariate analysis was not performed due to the limited sample size. Because the male subgroup was small ($n = 8$), age-related effects were evaluated across the entire cohort. Statistical significance was set at $p < 0.05$, and analyses were performed using SPSS software, version 28.0 (IBM, New York, USA).

Sensitivity analyses were not conducted due to the limited sample size and the exploratory design of the study.

Results

The study included 53 patients (45 females and eight males) with a mean age of 35 years (range: 15–82). Secondary acrocyanosis was diagnosed in 24 patients, representing 45.3% of the study population (Table 1). The conditions associated with secondary acrocyanosis are summarized in Table 2.

Advanced age was a significant risk factor for secondary acrocyanosis. Patients 40 or older had a relative risk of 2.5 (95% confidence interval: 1.4–4.5) compared to those under 40 (Table 3). Absolute risk was not calculated because only relative risk estimates were used in this study; the confidence interval was relatively wide due to the limited subgroups sizes.

No statistically significant difference in the prevalence of secondary acrocyanosis was observed between sexes, although a

Table 2 | **Secondary acrocyanosis ($n = 24$) by disease and subtype.**

Disease category	Subcategory	*n*
CTD	UCTD	12
	Lupus erythematosus	2
	Sharp syndrome	1
	Mixed connective tissue disease	1
	Sjögren's syndrome	1
Drug-induced	Beta blockers	3
Neurological	Myelopathy	1
	Parkinsonism with Shy–Drager syndrome	1
	Multiple sclerosis	1
APLA*		1

*Only antiphospholipid antibody positivity was observed, without a definitive diagnosis of antiphospholipid syndrome. These antibodies remained positive on serial testing.
CTD = connective tissue diseases, UTCD = undifferentiated connective tissue disease, APLA = antiphospholipid antibodies.

Table 3 | **Risk of secondary acrocyanosis by age and sex.**

	RR (95% CI)	*p*-value
Age ≥ 40 vs. < 40	2.5 (1.4–4.5)	0.002
Male vs. female	1.5 (0.8–2.8)	NS

RR = relative risk, NS = not significant, CI = confidence interval.

Table 1 | Patients with primary and secondary acrocyanosis: number and percentage by age and sex.

	Primary acrocyanosis		Secondary acrocyanosis		Total
	n	%	*n*	%	
All patients	29	54.7	24	45.3	53
< 40 years old	24	70.6	10	29.3	19
≥ 40 years old	5	26.3	14	73.7	8
Male	3	37.5	5	62.5	53
Female	26	57.8	19	42.2	34

higher frequency was noted among males (62.5%) compared to females (42.2%). However, this difference did not reach statistical significance.

Discussion

The clinical presentation of primary acrocyanosis was first described by Crocq in 1896 (6). Over time, however, the term has been used inconsistently to describe a variety of peripheral cyanotic conditions, including those with necrosis, that deviate from the original definition (4, 7, 8). In 1966, Merlen introduced the distinction between primary acrocyanosis and other forms, which he referred to as secondary (9). In 2001, a two-group classification further refined this differentiation, establishing two clinically distinct profiles analogous to those recognized in Raynaud's phenomenon (10). The features of primary acrocyanosis described in the literature—typically affecting young women, onset before age 30, bilateral and persistent cyanosis, absence of trophic disorders, underweight habitus, and otherwise normal examination findings—remain consistent across studies.

In a previous investigation, secondary acrocyanosis associated with CTDs accounted for 8% of total cases (9/108) and 53% of secondary forms (9/17). In our study, CTDs represented 32% of all cases (17/53) and 71% of secondary forms (17/24). Data comparing the prevalence of secondary and primary acrocyanosis remain limited in the literature.

The only available study reporting this comparison (10) found that secondary forms accounted for 16% of total cases (17/108), a proportion the authors considered small. Other studies, in contrast, suggest that primary acrocyanosis is relatively rare and that secondary forms are more frequent, although they often lack quantitative analysis (11–13). This inconsistency likely reflects the inclusion of cases that deviate significantly from the typical presentation—particularly acute-onset cyanosis or necrosis secondary to occlusive macro- and microcirculatory diseases—which should not be classified as acrocyanosis.

In this study, as in that by Planchon et al. (10), inclusion criteria (purplish cyanosis and cutaneous hypothermia of the hands) excluded recent-onset cyanosis due to occlusive vascular diseases (arterial, arteriolar, and venous) or paroxysmal manifestations typically associated with CTDs. Therefore, only medical cases with hypothermia and persistent cyanosis for at least 2 months were included for differential diagnosis, excluding conditions that deviate significantly from the typical presentation.

The prevalence of secondary acrocyanosis in our cohort (45.3%) was substantially higher than that reported in the limited literature and observed in clinical practice over past decades. Several factors may explain this difference. First, the study was conducted at specialized secondary care centers, potentially introducing selection bias toward patients presenting with clinical features indicative of the condition. In primary care, where physicians generally do not have access to advanced diagnostic tools (such as videocapillaroscopy), referrals are likely to be less selective.

A second possible explanation relates to environmental factors. Over the past 2 decades, rising average temperatures and milder winters may have contributed to a decline in primary acrocyanosis. Previous studies have demonstrated that primary acrocyanosis is less prevalent in warmer climates, becoming almost exceptional in the subtropical climate of South Carolina (2). Consequently, as the incidence of primary acrocyanosis decreases, the relative proportion of secondary forms may appear to increase.

Regarding instrumental assessment (e.g., color Doppler ultrasonography, continuous-wave Doppler, and plethysmography), the literature indicates that inspection of arterial vascularization is rarely required to confirm the diagnosis (10). Nailfold capillaroscopy is typically reserved for cases with Raynaud's phenomenon or paroxysmal cyanosis (10).

The typical presentation of primary acrocyanosis is characterized by capillary-venous stasis, with a purplish base and prominent capillary peaks. Ectasia is evident on both the capillary apex and venous side (up to 30 microns), whereas the arterial side remains relatively attenuated. Blood flow is slow, stagnant, and granular in appearance. These typical capillaries show variable density, ranging from numerous to reduced, and may at times be completely absent (14). The subpapillary venous plexus often appears prominent due to dilation and reduced skin thickness, sometimes associated with mild edema. In individuals with hyperhidrosis, small sweat droplets may be observed (15–17).

However, capillaroscopy may be a source of diagnostic confusion for less experienced operators, particularly in the presence of pronounced capillary-venous dilation and associated edema. This may lead to misinterpretation as an organic microangiopathy of the scleroderma pattern (4, 10, 18). In the literature, this instrumental examination is generally considered supportive but not essential (4, 19).

The diagnosis of primary acrocyanosis is generally considered easy and primarily clinical, relying solely on objective examination of the hands (20). It most commonly occurs in adolescents and young women, particularly those that are tall, thin, and occasionally anorexic (18, 19, 21). In such typical cases, additional investigations are often deemed unnecessary. However, some authors have recently argued that primary acrocyanosis, considered rare, should be regarded as a diagnosis of exclusion and may require ancillary investigations (11).

In contrast, other studies suggest that primary acrocyanosis is the most common acrosyndrome (2). In our cohort, we observed a relatively high prevalence of secondary acrocyanosis, particularly in the context of CTDs (22–24), exceeding previously reported frequencies. These findings suggest that secondary forms, especially those associated with CTDs, may be more common than previously recognized.

These results should be interpreted cautiously due to the limited sample size and the specialized clinical settings in which participants were recruited. Nonetheless, the findings may be relevant for primary care clinicians managing patients with suspected acrocyanosis.

Conclusions

To mitigate potential misdiagnosis, we recommend that patients with clinical suspicion of secondary acrocyanosis—particularly in cases suggestive of CTDs—be referred to specialized secondary care centers, where routine nailfold capillaroscopy and ANA testing can be performed.

For patients initially assessed in non-specialized primary care settings, referral to a secondary care center is advised if the clinical presentation suggests a possible secondary form. Preliminary blood tests, including ANA testing, which are now widely available, may be performed to support the clinical suspicion of a secondary form and assist in early identification.

Overall, the increasing recognition of secondary acrocyanosis, particularly in association with CTDs, underscores the need for

further studies in larger and more diverse populations to better define its prevalence, clinical characteristics, and optimal diagnostic strategies.

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