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Review Article

Acrocyanosis – A Symptom with Many Facettes

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Abstract

Acrocyanosis is an uncommon complaint belonging to the acro-syndromes. It typically presents with coolness and bluish discolourations of hands, feet, ears, nose, lips and nipple. The most frequently affected parts of the body are the hands. This review discusses physical factors, vascular disorders, infectious diseases, haematological disorders, solid tumours genetic disorders, drugs, eating disorders, and spinal disease presenting as or leading to acrocyanosis.

Introduction

Acrocyanosis is an uncommon complaint belonging to the acro-syndromes. It typically presents with coolness and bluish discolourations of hands, feet, ears, nose, lips and nipple. The most frequently affected parts of the body are the hands. Discoloration and coolness may be permanent or temporary and the result of a peripheral functional vascular disease and reduced tissue oxygenation. A great variety of conditions and disorders may be responsible for acrocyanosis [1]. Chronic idiopathic has been identified as a cutaneous sign of a "latent" cardiovascular risk [2].

Physical factors

Cold can induce vasospasm of digital arteries and arterioles resulting in acrocyanosis. The major differential diagnosis is perniones (chilblains) [3]. Sojourn in high altitude can cause some systemic diseases. From a dermatological point of view, acrocyanosis is a possible consequence due to the combination of lowered oxygen pressure, wind and cold temperatures [4].

Vascular disorders

Raynaud's phenomenon is the most common underlying cause of acrocyanosis. It is characterised by paroxysmal reversible episodes of vasospasm, usually involving small peripheral vessels of the fingers or toes and resulting in a triple-colour change starting with pallor and followed by cyanosis and erythema. Attacks are typically triggered by cold or

emotional stress [5].

Primary Raynaud's syndrome must be differentiated from secondary Raynaud's phenomenon seen in scleroderma, mixed connective tissue disease, dermatomyositis, systemic lupus erythematosus or anti-phospholipid syndrome [6][7].

Thoracic outlet syndrome is a compression of the neurovascular structures in the area superior to the first rib and posterior to the clavicle. Paget-Schröetter syndrome is an effort-induced thrombosis of the upper extremity. It is the leading vascular disorder in male athletes. The combination of both disorders can either lead to painful or painless acrocyanosis [8][9][10].

Primary vasculitis, such as giant cell arteritis, granulomatosis with polyangiitis, or essential cryoglobulinemic vasculitis, can lead to peripheral ischemic manifestations including acrocyanosis [11].

Infections

Chikungunya is a mosquito-borne viral infectious disease that has emerged as a global pathogen. Three to seven days after mosquito bite fever, rash, severe joint and muscle pains, and arthritis develop. It can spread vertically from mother to unborn child. Neonates infected intrauterine with chikungunya present with severe symptoms and infrequently death. Acrocyanosis progressing to ischemic digits is a typical symptom [12].

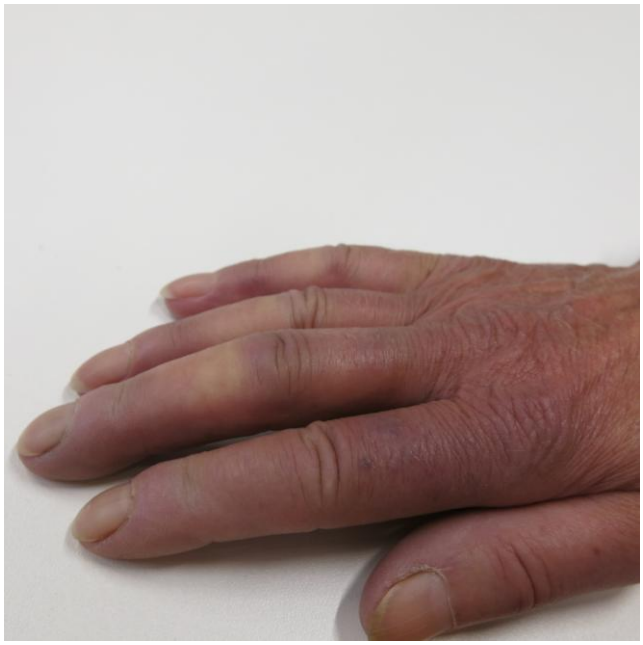

Figure 1: Acrocyanosis in a 74-year-old female with a herniated disk of the cervical spine. The differential diagnosis includes scleroderma, but sclerodactylia is absent

In rare cases of parvovirus B19 infection or lepromatous leprosy, acrocyanosis has been observed [13][14].

Persistent acrocyanosis with skin atrophy is a possible sign of late borreliosis – acrodermatitis chronic atrophicans (Herxheimer) [15].

Hematologic disorders

Cold agglutinin disease is a rare disorder with typical cutaneous signs such as livedo reticularis of the thighs, acrocyanosis and Raynaud's phenomenon upon cold exposure [16].

In rare circumstances, chronic lymphocytic leukaemia can be associated with cold agglutinin disease [17]. Acrocyanosis has been observed in Hodgkin's disease [18].

Essential thrombocythemia is a myeloproliferative neoplasm characterised by an increase in blood platelets. The most common cutaneous sign is itching, acrocyanosis, erythromelalgia, livedo reticularis, and Raynaud's phenomenon are rare but possible manifestations [19].

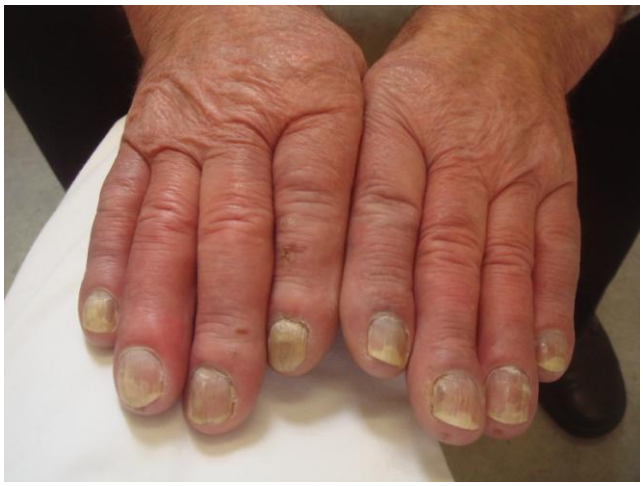

Figure 2: Peripheral sensory diabetic neuropathy with acrocyanosis and onychomycosis in a 78-year-old male

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes) syndrome is a rare systemic disease with the monoclonal proliferation of plasmacytes and slow progression. Cutaneous alterations are present in two-third of patients with diffuse cutaneous hyperpigmentation, and acrocyanosis [20].

Solid tumours

Acrocyanosis can be a rare symptom of extra-adrenal pheochromocytoma [21], intrahepatic carcinoid tumour [22], or endometrial adenocarcinoma [23]. This phenomenon has also been described under the terminus “paraneoplastic acral vascular syndrome” [24].

Genetic diseases

Aicardi-Goutières syndrome (AGS) caused by mutations in the *SAMHD1* gene is characterised by early-onset encephalopathy and chilblains. Additional findings include acrocyanosis and Raynaud's phenomenon [25].

Ethylmalonic encephalopathy is a rare metabolic disorder caused by mutations in the *ETHE1* gene. Neurodevelopmental delay and regression, pyramidal and extrapyramidal involvement, episodes of acrocyanosis, recurrent petechiae and chronic diarrhoea are cardinal features of the disease. Characteristic metabolic findings include lactic acidemia, elevated plasma C4 and C5 acylcarnitines, C4 and C5 acyglycines, and substantial ethylmalonic aciduria [26].

Other possible underlying genetic diseases of acrocyanosis include fucosidosis, and oxaliosis [27][28][29].

Drug-induced

Ergot alkaloids used for the treatment of headaches and migraine can cause acrocyanosis and hand or leg ulcers [30]. Particular attention has to be paid in case of antiretroviral therapy since alkaloid action can be potentiated due to an inhibition of cytochrome P450 [31].

Liposomal amphotericin-B and amphotericin-B deoxycholate used for the treatment of systemic fungal infections have been reported to cause acrocyanosis that was reversible after discontinuation [32][33].

A bilateral foot acrocyanosis developed in a patient suffering from multiple sclerosis during interferon-β-treatment [34].

Tumescent liposuction for liposuction is known to cause acrocyanosis as a possible adverse effect. In severe cases, cyanosis, tachypnea, tachycardia, hypotension, confusion, or even death may be observed. Methemoglobinemia has been noted with all anaesthetics, such as lidocaine, prilocaine or ripivocaine, and patient safety demands laboratory monitoring of methemoglobin [35].

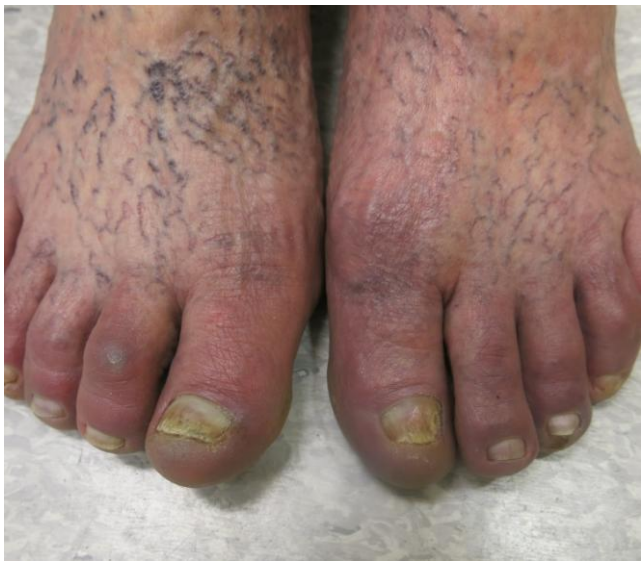

Figure 3: Acrocyanosis in a 71-year-old female after partial pulmonary resection due to malignant pheochromocytoma. The lesions developed with a delay of several months

Digital ischemia with acrocyanosis is a rare event during intravenous chemotherapy with gemcitabine, cisplatin or oxaliplatin [36]. Other drugs known to induce acrocyanosis are metoclopramide, imipramine, desipramin, and fluoxetine [27].

Eating disorders

Acrocyanosis is a possible cutaneous symptom of anorexia nervosa and bulimia nervosa due to persistent vasoconstriction associated with impairment of thermoregulation and reduced and delayed responsiveness to both vasodilator and vasoconstrictor agents [37][38].

Spinal disorders

Japanese authors described two male patients with cervical myelopathy, which exhibited peculiar vasomotor symptoms ("acro-erythro-cyanosis"). Continuous reddening, swelling and skin temperature increase were observed on both hands and feet or both hands. Cold stimulation resulted in paroxysmal cyanosis and a decrease in skin temperature [39].

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