

## Rare Case of Vasospastic Acute Limb Ischemia: Secondary Raynaud's

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### Abstract

**Background:** Acute limb ischemia (ALI) requires immediate treatment to maintain limb viability and prevent morbidity and mortality. Nevertheless, vasospastic acute limb ischemia on limb arteries is rarely reported.

**Case illustration:** This article reported a 37-year-old woman with sudden pain in her left leg and foot. The absence of peripheral pulsation of the left dorsalis pedis artery and popliteal artery were noted. Her foot was cold and clammy with decreased oxygen saturation in the left toes. The symptoms were partially improved following heparinization therapy. Angiography was conducted, and it revealed the spasms of the left popliteal and dorsalis pedis arteries with no sign of acute embolism or thrombosis. Arterial vasospasm is a rare cause of acute limb ischemia. A theoretical etiology of this vasospasm might be a secondary Raynaud's phenomenon. The associated factors were female, pre-menopausal age, the use of combined injectable contraception containing estrogen, and exposure to cold temperatures.

**Conclusion:** This case report emphasizes the necessity to consider all possible causes in ALI-presenting cases to provide adequate therapy and prevent limb death.

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## Introduction

**A**cute limb ischemia (ALI) is a critical vascular emergency on the peripheral artery that requires immediate treatment to maintain limb viability and prevent morbidity and mortality. The etiology is largely due to arterial embolism, thrombosis, or traumatic injuries.<sup>1</sup> Nevertheless, vasospastic acute limb ischemia on limb arteries is rarely reported.<sup>2</sup> This article reported a case on a young woman presenting ALI with documented vasospasm on cold exposure.

## Case Illustrations

A 37-year-old woman was referred with sudden pain in her left leg and foot 8 hours before admission. The pain started as a mild tingling sensation followed by continuous sharp-shooting pain. From two years prior, she had experienced several intermittent pain episodes triggered by cold exposure. The patient lived in a foothill and was almost constantly exposed to the cold weather, particularly during the rainy season. She had never considered having it checked as the pain always improved after resting. When this pain started as she was exposed to the cold weather, she expected it to resolve as usual. Instead, this pain got intensified. She also admitted that she had uncontrolled diabetes mellitus and had been using monthly combined injectable contraception containing estrogen for the last two years. She denied any history of hypertension, heart disease, tobacco exposure, trauma, or drug abuse.

Upon her arrival, her blood pressure was 100/60 mmHg and her pulse rate of 94 beats/min (regular rhythm). She had a normal body mass index (body weight 51 kgs – body height 150 cm). Head, neck, thorax, and abdomen were within normal limits. Peripheral pulsation of the left dorsalis pedis artery and popliteal artery were absent. Her left foot was cold, clammy, with pale toenails, and a blue-colored foot. Pulse oximetry reading on the toes were the following 89%, 88%, 84%, 88%, dan 90% (I, II, III, IV, V) (**Figure 1**). Both her electrocardiography and chest X-ray were unremarkable. Neurologic examination showed decreased motoric and sensory function below the ankle. Doppler ultrasound and DSA were not immediately available.

Laboratory data consisting of complete blood

count, liver - renal function, and lipid profile revealed no abnormality. Random glucose test upon admission was 214 mg/dL. Based on the history, risk factors, and physical examination, the initial diagnosis was acute limb ischemia grade IIB. As the case had a neurological deficit, she immediately received unfractionated heparin treatment and analgesia (IV metamizole). Unfractionated heparin 4.000 IU bolus was given and would be followed by continuous 19.000 IU heparin for 24 hours. Following therapy, the symptoms were partially improved and the dorsal artery pulse was positive but faint.

However, in less than 24 hours, the resting pain re-intensified. Angiography was immediately ordered to consider further therapy and preserve the limb. It revealed two spasms of the left popliteal and dorsalis pedis arteries. No sign of acute embolism or thrombosis was present (**Figure 2**). The spasm resolved after patient received nitrate intra-arterial during angiography. Post angiography, heparin infusion was discontinued. The patient then received nifedipine slow-release 30 mg daily, aspirin 75 mg daily, beraprost sodium thrice daily, atorvastatin 20 mg daily, and ramipril 2.5 mg daily. The symptoms resolved and the physical findings fully normalized. She was recommended to avoid cold exposure, switch to non-estrogen combined injectable contraception method, and have a better control for her diabetes mellitus. No recurrences on vascular event were reported in the follow up visit a month after discharge.

A wide range of vasospasm etiologies was evaluated. Raynaud's phenomenon was the most likely considering that the symptoms were started since she received estrogen-containing and cold exposure triggers the symptoms. Nevertheless, the exact cause of the vasospasm was still unknown. Her final diagnosis was vasospasm leading to acute limb ischemia suspected secondary Raynaud's phenomenon

## Discussions

Acute limb ischemia (ALI) is a sudden decrease in limb perfusion occurring in less than 14 days. Thrombus and emboli are mostly responsible for the majority of ALI cases. However, apart from these causes, ALI could also be originated from several conditions such as trauma, ergotism, iatrogenic complications, popliteal artery entrapment syndrome, and hypercoagulability.<sup>1</sup>

Iatrogenic causes are infrequent, i.e. the use of ergotamine drugs, LSD, or occur spontaneously. The TransAtlantic Inter-Society Consensus (TASC) also proposed embolism and atherosclerosis as the main causes, but both are rarely found in young adults.<sup>3</sup>

Arterial vasospasm is a rare cause of ALI. There were only a few reported cases of spontaneous vasospasm. A study by Kuchynkova et al reported a rare case of a 19-year-old patient with prolonged vasospasm resulting in a clinical presentation of ALI. The condition had no clear cause and history that might support atherosclerosis.<sup>2</sup> Another case by Winckiewicz et al presented a 20-year-old woman with sudden pain in her right foot. Her foot was pale and cold along with paresthesia and weakness. Following a detailed examination, it was also suspected that artery spasms might be the cause.<sup>3</sup> Both cases indicated that in some cases, spontaneous vasospasm could be the etiology of ALI.

Vasospasm may result from constriction of arterial smooth muscle. One of the causes of vasoconstriction is Raynaud's phenomenon. This phenomenon is caused by an exaggerated response in the form of vasospasm mostly triggered by cold temperatures or emotional stress. This disease can be idiopathic or secondary to other conditions, such as rheumatology or autoimmune diseases, namely scleroderma, systematic lupus erythematosus, rheumatoid arthritis, dan polymyositis), arterial disease (peripheral artery disease and Buerger diseases), neurological (carpal tunnel syndrome, stroke), blood disorders (multiple myeloma), trauma (use of vibrating work tools, and frostbite), as well as some endocrine disorders (use of beta-blockers, amphetamines, narcotics, drugs chemotherapy, estrogen, and clonidine). Raynaud's phenomenon may range from mild benign vasospasm to severe digital ischemia that might threaten tissue viability.<sup>4-6</sup>

The actual cause of vasospasm, in this case, was unknown. A history of intermittent pain episodes related to cold temperature was one of the important details reported by this patient. However, as primary Raynaud's phenomenon usually occurs between the ages of 15 and 25, anyone over the age of 30 should be evaluated for secondary Raynaud's phenomenon. The patient did not utilize any precipitating medicines such as ergotamine, LSD, or beta-blockers. Nevertheless, the intermittent pain episodes were noticeable after she started using monthly injectable contraception. The

active ingredients in monthly injectable contraception are medroxyprogesterone acetate and estradiol cypionate (Cyclofem™) or norethisterone enanthate and estradiol valerate (Mesigyna™). Both preparations contain estradiol.

Very few studies reported any role of estrogen-containing contraception in limb arterial vasospasm. Still, Raynaud's phenomenon is highly associated with estrogen (17 $\beta$ -estradiol). It was known that females predominated most of Raynaud's phenomenon cases in the US.<sup>7</sup> Moreover, the ratio of premenopausal women was even higher than post-menopausal women.<sup>8</sup> Thus, it concluded that estrogen might play roles in it. Post-menopausal women who received estrogen replacement therapy were also more likely to have Raynaud's phenomenon than those who did not. Other evidence suggested that estrogen (17 $\beta$ -estradiol) influenced vasoconstriction by increasing the expression (activating the  $\alpha$ 2C adrenoreceptors gene promoter), localization, and function of  $\alpha$ 2C adrenoreceptors in vascular smooth muscle cells. This receptor had been found mediating the cold-induced vasoconstriction in mice models. The cold would trigger sympathetic activity reflex leading to vasoconstriction via norepinephrine.<sup>9</sup> These findings suggested an association between estrogen and Raynaud's phenomenon. It was thought to increase the response of premenopausal women to cold air and the higher prevalence rate of RP in younger women. Another study by Fraenkel et al on 497 postmenopausal women found 49 women had Raynaud's phenomenon. The prevalence of Raynaud's phenomenon among women who received estrogen alone (19.1%) and estrogen-progesterone (9.8%) was not significantly different, with OR 2.5 and 0.9, respectively. They concluded that Raynaud's phenomenon was associated with unopposed estrogen therapy.<sup>10</sup> Whether any additional exposure of estrogen in premenopausal women might precipitate Raynaud's phenomenon was yet to be investigated in the future.

The symptoms in our case showed signs of ALI grade IIB. The grading was based on Rutherford's ALI classification (sensory loss more than toes, resting pain, and moderate muscle weakness, however, without doppler ultrasound and DSA-not immediately available).<sup>1,11</sup> The previous health center recognized this patient to be in high risk for thrombotic/embolic ALI due to her history of uncontrolled diabetes mellitus. Diabetes mellitus is known to be one of major risk factor

of peripheral artery disease including ALI<sup>1</sup> due to its strong correlation with atherosclerosis. To prevent the disease progression, heparin and pain management was urgently given as recommended by *European Society of Cardiology*.<sup>1</sup> An intravenous injection of unfractionated heparin (50–100 units/kg) should be administered immediately following the diagnosis of ALI to prevent the second proximal and distal progression from the site of occlusion.<sup>12</sup> Hence, the main goal of heparin was to avoid propagation thrombus and worsening ischemia. Heparin also presented a less known vasodilatory effect aside from its anticoagulant properties. Several studies reported the vasodilatory effect on coronary arteries and human internal mammary arteries. These studies suggested that heparin had several vasodilatory mechanisms involving prostacyclin, nitric oxide (NO), and an unidentified endothelium-derived hyperpolarizing factor.<sup>13,14</sup> Therefore, this vasodilatory property of heparin might play a role in the transient improvement of the current patient.

Despite the transient improvement, the pain was re-intensified, and angiography was conducted in preparation for urgent revascularization (if needed). Instead of thrombosis/emboli, angiography confirmed vasospasms in both the popliteal artery and arteria dorsalis pedis. The three-color stage was inconspicuous. However, as previously noted, Raynaud's phenomenon does not require precise three stages to be identified.<sup>15</sup> It is concluded the theoretical cause of this vasospasm might be classified as a secondary Raynaud's phenomenon. Several supporting factors were female of pre-menopausal age, the use of combined injectable contraception containing estrogen, and presence of symptoms in cold exposure, and vasospasm feature presented by angiography. Medical management with proven efficacy was nifedipine (30 mg daily) and losartan (50 mg twice daily).<sup>11</sup> Calcium channel blocker had been the first line treatment of vasospasm (including Raynaud's phenomenon). Additional therapy included angiotensin receptor blocker, angiotensin converting enzyme inhibitor, aspirin, statin, selective serotonin reuptake inhibitors, and topical nitrates.<sup>6,11</sup>

There were several limitations in the present study. First, several additional tests were not performed on the patient (such as ANA, anti-dsDNA, and others) to exclude other etiologies due to financial reason. Raynaud's phenomenon is also highly associated with

autoimmune rheumatic diseases. It is worth noting that in several autoimmune rheumatic diseases, Raynaud's phenomenon was the first (or only) symptom/manifestation years prior to other features.<sup>15,16</sup> Second, this study only reported a short period of follow up of a potentially long-run disease. Future larger studies are needed to evaluate the association between ALI and Raynaud's phenomenon.

## Conclusion

In summary, this study emphasized the necessity to consider all possible causes in ALI-presenting cases to provide adequate therapy and prevent limb death. Further investigation on acute limb ischemia and Raynaud's phenomenon is needed to support the prevention and management of the disease.

## Publication Approval

All authors read and approved the final manuscript.

## Conflict of interest

None

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## Ethical Clearance

Not Applicable

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