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Acute Ischaemic Crisis of Raynaud Phenomenon in an Adolescent with Systemic Lupus Erythematosus

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Abstract Raynaud phenomenon is manifested as sudden vasoconstriction of distal phalanges with cyanosis and reactive hyperaemia. Ischaemic skin lesions are also noted in severe cases. We report a 17-year-old lady with systemic lupus erythematosus who presented with dry gangrene of digits owing to intense Raynaud attacks. Various management strategies are discussed.

Key words Adolescent; Ischaemic ulcers; Raynaud phenomenon; Systemic lupus erythematosus

Introduction

In Raynaud phenomenon, the distal phalanges become vasoconstricted and pale after exposure to coldness. The fingertips become cyanotic and reperfusion follows. These ischaemic attacks are usually episodic. Raynaud phenomenon can be classified as primary or secondary. We report an adolescent lady with severe Raynaud attacks in her fingers secondary to systemic lupus erythematosus.

Case Report

A 17-year-old lady presented with a two-week history of ischaemic ulcers affecting her right index, right middle and left index fingertips (Figure 1). She had had history of Raynaud phenomenon for two years and she had been diagnosed to have systemic lupus erythematosus for one year.

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Two years ago, she began to develop sudden pallor of all fingers and toes followed by cyanosis and erythema. These painful attacks occurred two attacks per day. No

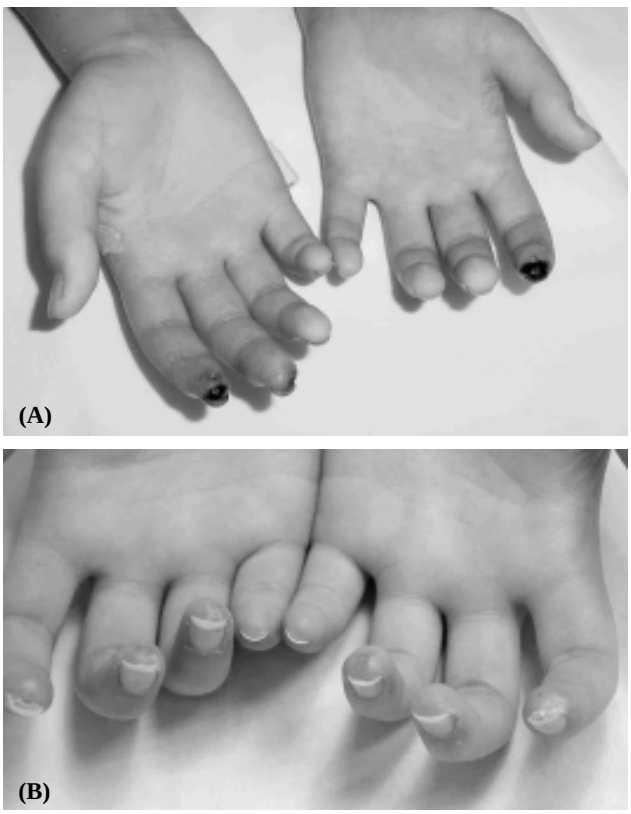

Figure 1 (A) Pre- and (B) post-treatment for acute ischaemic ulcers in fingertips due to Raynaud phenomenon.

precipitating factors were noted. Protective measures, including gloves in winter and attention to handling cold objects, were recommended. No medication was prescribed at this stage. High titre of anti-nuclear antibody (>1: 2560) with normal level of anti-double-stranded DNA antibody were found. Scleroderma-70 was negative. Her condition was regularly reviewed at the out-patient clinic.

Nevertheless, 11 months later, the attacks of Raynaud phenomenon were intensified with frequency increased from 2 times to 5 times per day. Nifedipine 5 mg three times per day was therefore commenced. The compliance remained poor and the control was unsatisfactory.

12 months after the original presentation of Raynaud phenomenon, she suffered from acute onset of fever, shortness of breath, orthopnoea and chest pain. She also developed malar rash. The Raynaud attacks stayed to be around 5 times per day. Echocardiogram confirmed the presence of pericarditis and pericardial effusion. High titres of anti-nuclear antibody (>1:2560) and anti-double-stranded DNA antibody (136 IU/ml) were noted. The levels of complements 3 and 4 remained normal. Diagnosis of systemic lupus erythematosus was established according to the American College of Rheumatology criteria of the classification of systemic lupus erythematosus. She was then treated by systemic steroid. The lupus activity was well controlled both clinically and biochemically. The severity of Raynaud attacks remained unchanged. Steroid therapy was then tailed down gradually.

Despite the introduction of nifedipine, the Raynaud condition worsened. She began to have difficulty in grasping objects like pencil and chopsticks. She was then admitted to the hospital two years after the initial presentation of Raynaud phenomenon for a two-week history of having dark and painful ulcers over three distal digits of her hands which were precipitated by minor trauma. The number of Raynaud attacks was also found to be doubled to 10 times per day on admission. Apart from the ulcers, she was clinically well. She had been treated with oral prednisolone 5 mg daily before this admission. Her anti-double-stranded DNA titre was 11 IU/ml, erythrocyte sedimentation rate was 35 mm/hr, C-reactive protein was <7 mg/L and the levels of complements 3 & 4 were normal. Both anti-cardiolipin antibody and lupus anti-coagulant were absent.

During the hospital stay, she received daily intravenous infusion of prostaglandin for five days with close monitoring of blood pressure and vital signs. Prostaglandin E1 (*Alprostadil*) 60 micrograms was infused once a day on Day 1 and 2 followed by a daily intravenous infusion of prostaglandin I (Prostacycline, *Ilprost*) for the next three days. Prostaglandin I was commenced at 1.1 ng/kg/min for 6 hours. It was stepped up to 1.8 ng/kg/min for 6 hours on the next two days. When she was put on a higher dose of prostaglandin I, she experienced mild headache and facial flushing during drug infusion. These side effects were lessened by reducing the infusion rate to 1.48 ng/kg/min. Her blood pressure had been kept stable all along. Apart from drug treatment, expert advices from various clinical disciplines were sought. The occupational therapist prepared a pair of thick gloves and a pair of heavy footwear (Figure 2). An electric warmer was used to keep her body warm. Wound dressing with povidine iodine and Mupirocin cream was performed twice daily. Topical nitroglycerine cream was applied to the ulcers as well. The orthopaedic surgeon was consulted who planned to perform localised digital sympathectomy if the condition did not get better. With all these measures, improved perfusion was noted over her fingertips with fewer vasopressive attacks which were reduced from 10 times to 5 times per day. There was no

Figure 2 Thick gloves and heavy footwear made by the occupational therapist.

secondary bacterial infection of the wounds. She was finally discharged with the slow release preparation of nifedipine (*Adalat Retard*) 20 mg twice daily and prednisolone 5mg daily after 11 days of hospitalisation. Abstinence from smoking was advised. A drug card advising to avoid the sympathomimetic drugs, clonidine, ergotamine and serotonin-receptor agonists was offered as well.

During the subsequent out-patient consultations, nifedipine was changed to the extended-release form (*Adalat GITS*) 60 mg daily as there were persistent attacks which were around 5 times per day. No hypotension or dizziness was experienced. Regular wound dressing and assessment by the wound nurse was performed. Protective measures were strongly encouraged. The number of intense and painful Raynaud attacks was further reduced to twice per day after the dose of nifedipine had been stepped up for one week. The dry gangrenous wound of her three digits healed completely 6 months after the initial presentation (Figure 1). Nifedipine and the conservative management were continued. Her condition was periodically reassessed at the out-patient clinic. She could cope with the normal daily living well.

Discussion

Raynaud phenomenon was first recognised by Maurice Raynaud in 1862.[1] The prevalence of Raynaud phenomenon in children aged 12-15 years was reported to be 15% in one study done in Manchester.[2]

Raynaud phenomenon is a clinical diagnosis, characterised by recurrent attacks of sharply demarcated pallor and then cyanosis of the skin of the digits after exposure to coldness.[3] The attack is then ended with reperfusion of the tips of the digits which is manifested by cutaneous erythema. Raynaud phenomenon should be distinguished from acrocyanosis, a condition with persistent cyanosis of the extremities triggered by cold temperature. Raynaud phenomenon is related to increased platelet aggregation and activation, increased serotonin and thromboxane A release and defect in vasoregulation.[4]

Primary Raynaud phenomenon occurs when there is no underlying disorder. Secondary Raynaud phenomenon is associated with other diseases. The presence of severe and painful attacks, gangrene or ulceration of skin, asymmetrical involvement, specific autoantibodies, abnormal nail fold capillaries and unusual history or physical findings are suggestive of secondary Raynaud phenomenon.[3] The presence of anti-nuclear antibody has a relatively higher risk of developing an associated systemic disease.[4] The true risk of having low titre anti-nuclear antibody for predicting an underlying systemic disease in patients with Raynaud phenomenon remains unknown.[4] The presence of antibodies against specific autoantigens is more suggestive of a secondary cause. Patients with Raynaud phenomenon who are positive for anti-centromeres or anti-topoisomerase antibodies (Scleroderma-70) are more likely to develop scleroderma-spectrum diseases.[4] Apart from having anti-autoantigen antibody, distorted or anatomically abnormal capillaries are found among patients with secondary Raynaud phenomenon.[3,4] A complete history and physical examination is mandatory for all patients with Raynaud phenomenon. Having fever, weakness, weight loss, rash, myalgia, arthralgia, arthritis and cardio-pulmonary abnormalities are highly suspicious of contracting a systemic disease.[3] If a secondary cause is suspected, the patient is likely to develop clinical or laboratory signs within two years.[3]

In our case, the lady initially had a high titre of anti-nuclear antibody but normal anti-double-stranded DNA antibody titre. Scleroderma-70 was negative. No capillaroscopic examination was performed. Around one year after having Raynaud phenomenon, she developed serositis, malar rash, persistently high anti-nuclear antibody titre and a raised anti-double-stranded DNA antibody titre. All these pointed to a secondary cause of Raynaud phenomenon: systemic lupus erythematosus.

The most frequent association of Raynaud phenomenon is scleroderma.[4] Ninety percent of patients with scleroderma have Raynaud phenomenon.[4] Secondary Raynaud phenomenon is found in around 30% of patients with systemic lupus erythematosus.[4] Raynaud phenomenon is not included in the American College of Rheumatology classification criteria for systemic lupus erythematosus. It is neither included in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[5] nor in European Consensus Lupus Activity Measure (ECLAM).[6]

For patients with mild vasopressive attacks, preventive measures are all needed. Keeping the whole body warm by wearing layers of clothings, stockings, headwear, footwear and gloves in cold weather is the main tactic.[3,4] Avoiding agents that can cause vasoconstriction is also essential (e.g. sympathomimetic drugs, clonidine, ergotamine and serotonin-receptor agonists).[3,4] Abstinence from smoking to prevent nicotine induced vasospasm is highly encouraged.[3,4]

In addition to the non-pharmacological supportive measures, vasodilating therapy can be added as well.

Primary Raynaud phenomenon with normal capillary has better response to vasodilating therapy whereas secondary Raynaud phenomenon with vascular structural damage has poorer response.[4] Calcium-channel blockers with some anti-platelet property appear to be the best available vasodilating agents in treating Raynaud phenomenon.[4] In a meta-analysis of placebo-controlled studies of calcium-channel antagonists for the treatment of Raynaud phenomenon in patients with scleroderma, it was found that such agents could moderately reduce the severity and frequency of attacks.[7] Among various calcium-channel blockers, nifedipine, which has selectivity for vascular smooth muscle, is the preferred drug.[4] If one single calcium-channel antagonist is not useful, there is no evidence to support the use of another one.[3]

Our patient was initially given nifedipine 5 mg three times per day. Due to poor compliance, the control was unsatisfactory. After the ischaemic crisis, we finally put her on the extended-release form of nifedipine *(Adalat GITS)* 60 mg daily. Reduced severity and frequency of vasopressive attacks were reported probably ascribed to an improved drug compliance.

Other agents, including angiotensin II receptor antagonists (e.g. losartan), serotonin re-uptake inhibitor (e.g. fluoxetine), alpha 1-adrenergic receptor blocker (e.g. prazosin) are probably useful.[4] Topical nitrates can be of some benefit.[4] However use of topical nitroglycerine in this case did not demonstrate prominent clinical improvement. For the use of anti-thrombotic agents, anti-coagulation therapies and anti-platelet agents such as aspirin, more definite data is necessary to prove the effectiveness of their usage.[4]

Raynaud phenomenon with acute ischaemic crisis should warrant early evaluation and administration of vasodilating therapy. There is evidence that intravenous prostaglandin therapy is useful.[8,9] Prostaglandin I has additional anti-platelet effect: inhibition of platelet aggregation and adhesion. Side effects like facial flushing and headache are related to the vasodilating effect. Blood pressure should be closely monitored during drug infusion. The efficacy of oral bio-available formulation of prostaglandin remains controversial.[9,10] In this case, both intravenous prostaglandin E1 and prostaglandin I were tried. Blood pressure was well maintained. Side effects of mild headache and facial flushing were minimised by decreasing the rate of drug infusion. After prostaglandin infusion, our patient experienced fewer vasopressive attacks.

Apart from pharmacological treatment, surgery is reserved for refractory cases. In our case, localised digital sympathectomy was planned if there was no improvement with the preventive and medical measures.

Raynaud phenomenon is a life-long disease. Continuous monitoring and evaluation are necessary.

In conclusion, we report an adolescent lady having systemic lupus erythematosus presented with intense Raynaud attacks causing dry gangrene of digits. In this case, conventional measures like frequent wound dressing and assessment, protective measures to maintain both central and peripheral body temperature were essential elements in the treatment. The use of prostaglandin infusion and high dose extended-release preparation of calcium-channel blocker were found to be useful in alleviating the acute ischaemic symptoms and avoiding the need for surgery. Close monitoring was continued to look out for recurrence of acute ischaemic crisis of Raynaud phenomenon.

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