A Lady with Refractory Raynaud's Disease

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CASE SUMMARY

History

A 33-year-old lady presented with a six-year history of discoloration and pain of her fingers. The fingers turned white, blue, and then red on exposure to cold weather. Raynaud's phenomenon was diagnosed by a rheumatologist and improved with nifedipine. However, this was later stopped as she developed an allergic rash to nifedipine. She also had arthralgia involving the finger and knee joints. Other features included a facial rash, photosensitivity, erythematous papules on the hands and feet, and livedo reticularis.

Her condition worsened in the past two years. There were persistent pain and cold fingers, leading to restricted finger movements and digital ulcers. These conditions responded poorly to repeated courses of prostaglandin infusion and bilateral thoracoscopic cervical sympathectomy. Drugs including aspirin, persantin, diltiazam, felodipine, prazosin, lisinopril, pentoxifylline were not effective. Transcutaneous electrical nerve stimulation reduced the pain but the fingers remained cold. She later developed gangrene of her left little finger requiring amputation at the proximal interphalangeal joint.

Her current medications included prednisolone, hydroxychloroquine, amlodipine, pentoxifylline, brufen, cytotec, isordil and zopiclone.

Apart from a spontaneous abortion twelve years ago, her past health was good. She was a non-smoker and non-drinker, and previously worked as a clerk. She has an 11-year-old daughter. There was no significant drug history.

Examination

On examination, her fingers, hands and forearms were cold. Gangrenous ulcers were seen over her fingers (Figure 1). Her left little finger was amputated at the proximal interphalangeal joint. There was no pitted digital scar or nailfold capillary change. Cardiovascular system was normal and peripheral pulses were present.

Investigations

Complete blood picture, ESR, C-reactive protein and blood chemistry were normal. The highest titer of ANA was 1:80. Anti-ENA, anti-DNA, RF, C_3, anti-cardiolipin antibody, lupus anticoagulant, cold agglutinin and cryoglobulin were all normal. Chest radiograph revealed no cervical rib. Skin biopsy of the amputated left little finger showed extensive ulceration and gangrenous inflammation at the epidermis and dermis. There were secondary vasculitis and thrombosis of the adjacent vessels. Non-lesional skin showed no abnormality. There was no feature suggestive of cutaneous lupus erythematosus. Immunofluorescence for IgG, IgA, IgM, C_3 and fibrin were all negative. The histological diagnosis was consistent with gangrenous inflammation.

Diagnosis

The diagnosis was Raynaud's disease. There were insufficient features to satisfy the criteria of diagnosis of SLE or systemic sclerosis at this moment.

REVIEW ON RAYNAUD'S PHENOMENON

Definition

Raynaud's phenomenon was first described by Maurice Raynaud in 1862. Diagnostic clinical feature is episodic colour change (pallor, cyanosis, erythema) occurring in response to cold conditions and/or emotional stress. This involves the fingers but may also involve the toes, nose and ears. Primary Raynaud's

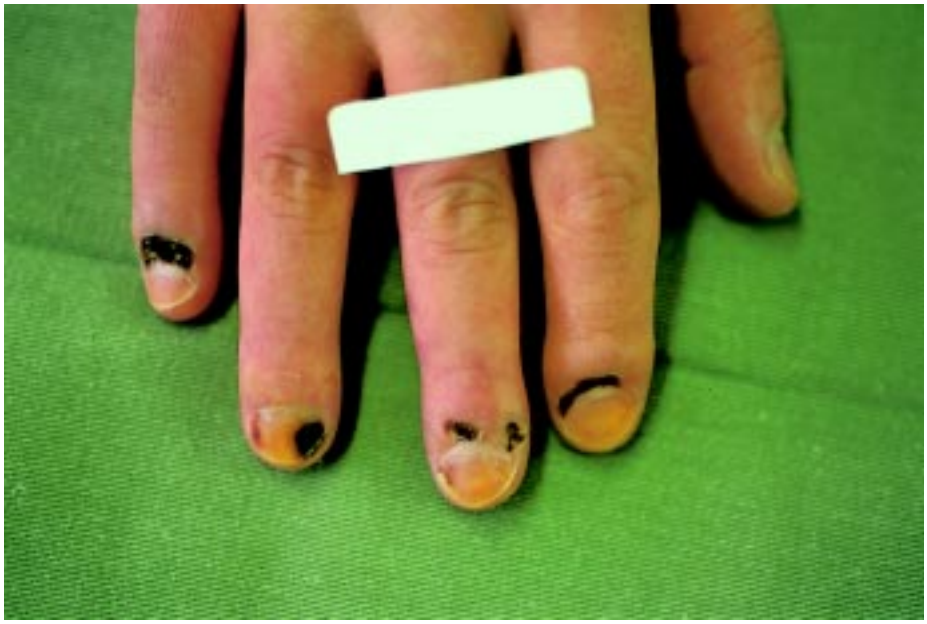

Figure 1: Multiple gangrenous ulcers on the fingers of right hand

phenomenon (Raynaud's disease) is defined as at least two years of symptoms without any apparent associated disease. The prevalence of Raynaud's phenomenon in the general population may be as high as 10-20%.

Causes

Causes of Raynaud's phenomenon include the followings:

1. Primary, also known as Raynaud's disease
2. Connective tissue disease: systemic sclerosis, systemic lupus erythematosis, polymyositis/ dermatomyositis, rheumatoid arthritis, overlap syndrome
3. Occupation and trauma: vibration
4. Thoracic outlet: cervical rib
5. Occlusive arterial disease: accelerated atherosclerosis, Berger's disease
6. Drugs or toxic substances: beta-blockers, ergot, oral contraceptives, bleomycin, polyvinyl chloride
7. Reflex sympathetic dystrophy
8. Hyperviscosity of the blood: cryoglobulinaemia, polycythaemia, paraproteinaemia

Pathogenesis

The pathogenesis is unclear but probably multifactorial. Deficiency of calcitonin gene-related peptide in perivascular nerves has been suggested as a possible cause. In systemic sclerosis, endothelial injury may cause platelet activation which leads to the release of vasoconstrictive substances (5-Hydroxytryptamine, thromboxane A2, adenosine di-phosphate).

Pathology

Histology is normal in mild cases. In more severe Raynaud's disease, there may be evidence of intimal hyperplasia, narrowing or total occlusion of arteries, or thrombosis.

Treatment

The majority of patients with Raynaud's phenomenon have mild disease. Treatment options are summarised as follows:

a) ***General:*** All patients should be advised to avoid cold conditions and smoking. They should use a hand warmer and thermal gloves. Moving to a warm climate alleviates symptoms in 50% of patients.

b) ***Pain:*** Pain control is important because pain can lead to additional vasospasm and more ischaemia. Narcotic analgesics may be needed.

c) ***Ulcer:*** Topical antiseptics and antibiotics are useful for healing of ulcers. Ketanserin has been reported to be especially good for treating ulcers. It has antiserotonergic and vasodilatory actions and also has an inhibitory effect on platelet-aggregability.

d) ***Calcium channel blockers:*** It is the first-line drug for Raynaud's phenomenon. Nifedipine 30 mg (up to 90 mg) daily decreases the severity of attacks by about 70-90% in 70% of the patients. Side effects include headache, palpitation, dizziness and transient flushing. Diltiazem but not verapamil may also be beneficial.

e) ***Nitroglycerin:*** At the cellular level, exogenous nitrates are converted to nitric oxide, which cause vascular relaxation and inhibit platelet aggregation. Sustained release glycero-trinitrate (GTN) patches (0.2 mg/hr.) placed on the chest wall for twelve hours a day can significantly reduce the number and severity of Raynaud's attacks. However, headache is a common problem.

f) ***Prostaglandins:*** Intermittent infusion of prostaglandin E, prostacyclin (PGI2), and iloprost (a prostacyclin analogue) should be considered in severe cases. It is given as a 5- to 10-day intravenous infusions for up to four to eight hours a day. Side effects include flushing, headache, nausea, and bradycardia. They act by preventing platelet aggregation. Another prostacyclin analog, beraprost sodium, was shown to be no more beneficial than placebo in a recent study.[1]

g) ***Calcitonin gene-related peptide (CGRP):*** It is an endogenous peptide with potent vasodilator effect produced by the calcitonin gene. It may be involved in the regulation of the peripheral circulation and its response to cold. CGRP in digital cutaneous perivascular nerves is deficient in patients with Raynaud's phenomenon. Intravenous CGRP has been shown to effectively dilate the compromised digital cutaneous vasculature in severe Raynaud's phenomenon.[2] Side effects include pronounced flushing, mild headache, diarrhoea and hypotension. However, it is not commercially available.

h) ***Transcutaneous electrical nerve stimulation (TENS):*** Low-frequency (2Hz) TENS has been reported to improve Raynaud's phenomenon, ulceration and pain in the feet, calcinosis and dysphagia in a patient with systemic sclerosis.[3]

i) ***Traditional Chinese acupuncture:*** In a German study with thirty-three patients with primary Raynaud's syndrome (17 treatment, 16 control), seven acupuncture treatments were given over a 2-week period.[4] The treated patients showed a significant decrease in the frequency of attacks from 1.4/day to 0.6/day ($P<0.01$). The overall reduction of attacks was 63% (control 27%, $p=0.03$). The beneficial effect lasted beyond 10 months after treatment without any side-effects. Acupuncture may act by causing a reduction in sympathetic tone and release of vasoactive mediators such as CGRP and substance P.

j) ***Autohaemotherapy:*** Autohaemotherapy has been used for the treatment of peripheral vascular disease in Germany without serious adverse effects. In an open trial, 4 patients with severe Raynaud's phenomenon (three had previously been refractory to iloprost) were treated daily or on alternate days for a two to three weeks period by re-injection of citrated autologous blood pre-treated with heat, ozone and ultraviolet light (H-O-U therapy).[5] There was a rapid and sustained improvement of the patients' condition and quality of life. Raynaud's attacks were reduced or abolished for at least three months after treatment. Immunomodulation may play a part in the beneficial response.

k) ***Surgery:*** Sympathectomy is now considered obsolete because of complications such as decreasing efficacy with time and poor response in patients with underlying arteriopathy.

l) ***Other treatment modalities:*** These include alpha-1 adrenergic blocker such as prazosin, reserpine (oral or infusion), angiotensin converting enzyme inhibitor, stanozolol (a fibrinolytic agent), evening primose oil and fish-oil capsules (containing omega-3 fatty acids) and plasmapheresis.

Progress

Within the first two years after onset, as many as

60% of patients will develop a connective tissue disease. Systemic sclerosis has the highest frequency of Raynaud's (95%). After many years of 'primary' Raynaud's phenomenon, around 5% of patients will develop a connective tissue disease, and almost all of them will develop CREST syndrome.

Learning points:

Nifedipine, a calcium channel blocker, is the first line treatment for Raynaud's phenomenon. It decreases the severity of attacks in 70% of patients.

References

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5. Cooke ED, Pockley AG, Tucker AT, Kirby DT, Bolton AE. Treatment of severe Raynaud's syndrome by injection of autologous blood pretreated by heat, ozonation and exposure to ultraviolet light (H-O-U) therapy. Int Angiol 1997;16:250-4.

Answers to Dermato-venereological Quiz on page 40

Answer (Question 1)

1. The practitioner has prescribed oral, systemic isotretinoin (Roacutane) of a dosage of 1mg/kg/day to the patient.

2. The clinical diagnosis is pyogenic granuloma induced by isotretinoin.

3. The preferred treatments include systemic corticosteroids in a dosage of 0.5-1 mg/kg/day for 4 weeks together with erythromycin 2 grams per day.

Pygoenic granuloma induced by isotretinoin is a rare but well documented adverse reaction of systemic isotretinoin. There are only 13 case reports so far in the world literature. It is more common in male patient who has taken systemic isotretinoin of a relatively high dosage. The condition is not life threatening but severely disfiguring. The exact pathogenesis is unknown but is believed to be due to the immunomodulating and tissue proliferating effects of systemic retinoids. The condition can be alleviated by systemic steroids therapy and oral erythromycin.

Answer (Question 2)

1. The clinical diagnosis is angiokeratoma circumscriptum involving the shaft of the penis.

2. The preferred treatment is either surgical ablation or laser therapy using CO_2 laser.

Angiokeratoma circumscriptum is a benign congenital condition that usually appears during puberty. The other forms of angiokeratoma such as angiokeratoma of Fordyce and angiokeratoma corporis diffusum (Fabry's disease) occur mostly in the scrotum and the buttock. Angiokeratoma corporis diffusum is a metabolic multi-system disorder that can result in renal or heart failure. One of the characteristic features of angiokeratoma circumscriptum is that the lesion can bleed easily while traumatised. The preferred treatment is surgical removal. CO_2 laser can give good cosmetic result.