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The role of the dermatologist in Raynaud's Phenomenon: a clinical challenge

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Abstract

Raynaud's phenomenon (RP) is a functional vascular disorder involving extremities. In his practice, the dermatologist may frequently encounter RP which affects mainly women and is categorized into a primary benign form and a secondary form associated with different diseases (infections, drugs, autoimmune and vascular conditions, hematologic, rheumatologic and endocrinologic disorders). Still today, the differential diagnosis is a clinical challenge. Therefore, a careful history and a physical examination, together with laboratory tests and nailfold capillaroscopy are mandatory. RP is generally benign but a scheduled follow-up for primary RP patients should be established, due to risk of evolution to secondary RP.

A combination of conservative measures and medications can help in the management of RP. The importance of avoiding all potential physical, chemical and emotional triggers, as well as quitting smoking should be strongly suggested to the patient. As first line treatment, dihydropyridine Calcium Channel Blockers should be used. If this approach is not sufficient, prostacyclin derivatives, phosphodiesterases inhibitors and endothelin receptor antagonists can be considered as second line treatment. In cases of acute ischemia nifedipine and intravenous prostanoidsare helpful. In refractory cases, botulinum injections have shown a significant benefit. The approach to the RP patients requires therefore a coordinated care of specialists together with the primary care physician.

Introduction

Raynaud's phenomenon (RP) is frequently encountered by the dermatologist in his practice and represents today a clinical challenge. It is defined as a bi- or tri-phasic color change of hands, feet, nose, earlobes and tongue, characterized by blanching (ischemia) followed by cyanosis (anoxia) and later by rubor (reperfusion) **(Figure 1)**. Pallor is the most specific sign and rubor is the least specific. RP can affect one or more digits; it is painful, intermittent, and lasts from few minutes to several hours. Currently RP is classified as a primary RP (pRP) that usually has a benign course, and secondary RP (sRP) that is associated with multiple etiologies.

The aim of our work is to focus on the main problems that the dermatologist may have in managing RP in clinical practice.

Frequency of Raynaud's phenomenon

The prevalence of RP is variable, ranging between 4%-15%. There are inconsistencies in the prevalence rate across geographical areas due to differences in the diagnostic methods, climate characteristics, and ethnicity within various populations (1). A higher prevalence of RP has been described in younger women. In a large USA study with a 16-years follow up, 9.6% of the women and 8.1% of men developed pRP (2). In another study, the population-based annual prevalence rates of RP was estimated as 3.6% for women and 1.4% for men, with women clearly having a higher risk for RP(3). The risk of RP was shown to increase consistently, yet modestly, with age (over 35 years), and decrease constantly with the decreased body mass index. (3)

Triggers

RP is usually triggered by an abrupt fall of temperature or by emotional stress. Moving from a warm environment to a colder one (outdoors in winter or air conditioned room in summer) can trigger RP attacks. There are many secondary triggers for RP – (i) cigarette smoking(4), (ii) medications (5), (iii) caffeine, (iv) occupations involving the constant use of vibrating tools or cold substances with an exponential increase in the risk after 12-years of work (3), (v) exposure to chlorinated and non-chlorinated solvents [acetone, toluene, xylene, etc.](6).

Approach to the evaluation of Raynaud's phenomenon

When a patient complains of blanching fingers followed by cyanosis and rubor, a methodological approach is required (**Figure 2**). The first step is to confirm the diagnosis of RP. This can be accomplished by a careful clinical history and physical examination. Most patients may not have active RP at the time of evaluation; thus it is helpful to verify RP by inspecting photographs taken by the patient at the time of an attack or by the use of color charts that enable the patient to confirm the typical color changes (7). The next step is to determine if RP is pRP or sRP: a detailed history to identify possible etiologies, a careful physical examination, laboratory tests and nailfold capillaroscopy (NC) are essential at this stage.

Primary RP is due to an exaggerated vasospastic response to cold or other stimuli and usually occurs in young women (8). It is characterized by symmetrical attacks of short duration (few minutes) in absence of any specific skin lesion (like digital ulcerations or scars), internal organ involvement or acral vascular complication. Apart from the history of RP upon exposure to any stimuli, the rest of the history and physical examination is usually unremarkable, including normal NC. (9)

Secondary RP may involve both hands and may be, at the very onset, affecting only one finger. Usually, it is painful and lasts longer than pRP. It is suspected when the symptoms' onset is over 30 years and/or complications occur [e.g. digital ulcers (DUs), pitting scars (8), secondary infection, tissue gangrene and auto or surgical amputation (10) (**Figure 3**)]. (Table **I** details the differences between pRP and sRP)
Personal history and clinical examination help in identifying potential causes of sRP (see **Table II**) – occupational and environmental factors, smoking, medications (**Table III**), symptoms and signs suggestive of a connective tissue disease (CTD), vascular disease, hematologic condition or infectious disease.
A targeted laboratory work-up (autoantibodies and other serologies) may be helpful in identifying the cause. Further investigations, when needed, are guided by clinical evaluation. (The differential diagnosis are summarized in **Table IV)**.

Since approximately 10 to 30% of RP patients can develop a CTD (11-13), it is important to establish a scheduled follow-up with laboratory tests (e.g. complete blood count, erythrocyte sedimentation rate, chemistry, and autoimmune panel). An abnormal baseline

NC and/or abnormal serology (antinuclear, anticentromere or anti-Scl70 antibodies) are the best predictors for this progression.

Among all CTDs, the most frequently developed disease is Systemic Sclerosis (SSc). (14) A study of 586 patients with RP without definite CTD reported that 12.6% developed SSc after a median duration of a 4-years follow-up. The presence of a scleroderma pattern at NC, and the presence of anti-nuclear (ANA), anti-centromere (ACA) and/ or anti topoisomerase-I antibodies (anti-Scl70) independently predicted the evolution to SSc(11). However, these signs together with puffy fingers suggest a diagnosis of very early SSc, thus warranting further investigation of internal organs (15). Therefore, patients with RP and abnormal NC or positive serology should be labeled as "at risk for CTD" and followed periodically for detecting the potential transition to CTD.

For what concerns other CTDs, a study of 3029 pRP patients reported that 37% of them developed CTD, the most frequent being an undifferentiated CTD (UCTD), followed by systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, overlap syndrome and systemic vasculitides. (14)

Role of imaging

Nailfold capillaroscopy (NC) is a very useful technique that can easily be performed with a stereomicroscope or an ophthalmoscope to identify microvascular changes suggestive of CTD. A scleroderma pattern (giant capillaries, micro-hemorrhages, architectural modifications and avascular areas) is typically found in SSc (**Figure 4**)(16) and in a good proportion of patients with dermatomyositis (DM), with a high sensitivity and specificity (14,17,18). In contrast, in other CTDs (polymyositis (PM), systemic lupus erythematosus (SLE), Sjögren syndrome (SjS), rheumatoid arthritis (RA) and systemic vasculitides normal capillaries or *non specific changes* (such as elongated or enlarged capillaries or a slight capillary loss), are generally found, and cannot therefore be considered as predictive of the disease (14). Interestingly, a lack of association was found between the clinically involved digits and the degree of alterations seen at NC (19).

When RP is asymmetric and tissue lesions are present in the digits, **Doppler ultrasound** may help to identify pathologic modifications of the arterial circulation, particularly in the ulnar arteries. However, the involvement of the digital arteries is difficult to demonstrate with Doppler, despite the fact that it is present in 63% of sRP and in 6% of pRP patients (20). In recurrent and complicated cases of sRP, conventional angiography or **Magnetic Resonance Angiography** (MRA) are the gold standard for the assessment of the

macrovasculature (21). These investigations are recommended to evaluate the potential of large to medium artery pathology, as seen in atherosclerosis, Takayasu vasculitis, and Buerger's disease. These disorders are characterized by limb claudication on exercise, asymmetric abnormalities or an isolated and persistent digital ischemia, that can mimic RP.

Role of outcome measures

There has been a great deal of interest in developing disease activity and outcome measures in the clinical trial setting (22). In RP clinical trials, patients are usually advised to maintain a diary to record the frequency and duration of RP attack, and at the end of each day they are advised to complete a Raynaud's Condition Score (RCS). The RCS is a daily self-assessment of RP activity using a 0–10 ordinal scale. RCS incorporates the cumulative daily frequency, duration, severity, and impact of RP attacks on hand function. Other measures include patient and physician assessments of RP. However, the efficacy of these outcome measures has been fairly variable largely due to the subjective nature of the measures and also due to the placebo effect. A combination of items has been shown to be associated with lower placebo responses (23).

Treatment of Raynaud's phenomenon

The initial management of RP aims to avoid RP triggers and to adapt lifestyle to patient's need (24). Patients are advised to avoid or minimize cold exposure and thermal excursions, to dress warm and to have adequate insulation during cold weather and to keep their hands and feet warm with gloves and appropriate footwear. It is important to emphasize the value of quitting smoking. Patients should try to avoid emotional triggers, physical or chemical triggers and medications thought to cause RP. In most cases of pRP, pharmacotherapy is not required and lifestyle modifications are sufficient may control the symptoms (25). In contrast, pharmacological therapy, single or combined, is often needed in sRP.

Pharmacological therapy

Recently, new recommendations have been issued focusing mainly on calcium channel blockers (CCBs), prostacyclin derivatives, Inhibitors of phosphodiesterases and endothelin receptor antagonists (25).

CCBs, especially dihydropyridine type CCBs, are the most commonly used group of medications as a first line treatment of RP. They relax vascular smooth muscle cells leading to vasodilation, and they also reduce platelet activation. They have been shown to reduce the number and severity of RP attacks and its complications. Nifedipine has been the most extensively studied (26) and recommended as the first line therapy to reduce the frequency and severity of RP in SSc patients (25). The newer second-generation CCBs (amlodipine, isradipine, nicardipine, felodipine) are also effective in reducing RP attacks. The treatment should start with a low dosage and titrated based on the tolerance and side effects in the individual patient. Common side effects of CCBs include headache, significant reduction of systemic blood pressure or peripheral edema. Based on the available evidence, oral CCBs like nifedipine or amlodipine should be used as initial choice of pharmacotherapy.

If the therapy with CCBs is not effective in controlling the attacks, other therapies are recommended (**Table V**) and an expert consultation should be obtained for further care. In patients who have to use a beta-blocker for cardiac indications, it is preferable to avoid the use of beta2-blockers (non-cardio selective) and use beta1-blockers (cardio selective) like carvedilol, labetalol and nebivolol although there are rare case reports of RP related to the use of beta1-blockers. (27,28). Gingko Biloba, herbal medications, acupuncture and other alternative therapies (laser and nutritional supplements) did not prove to impact the frequency, duration and severity of RP(29). Moreover, temperature biofeedback is reported to be less efficacious than nifedipine in treating RP (30). Recently, a pilot single-center, randomised controlled trial of acupressure versus targeted patient education in primary and secondary RP did not show any efficacy for this technique (31). Recently, the use of ischemic preconditioning, which was thought to help potentially patients with RP, reducing the number of attacks, was found ineffective (32)

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Emergencies in Raynaud's phenomenon- the threatened digit

Patients with chronic sRP, especially in the setting of CTD, can have episodes of acute digital or limb ischemia, which can rapidly progress to necrosis and gangrene. Early recognition and prompt vasodilating therapy is the key to avoid tissue loss. A detailed vascular examination is helpful; if peripheral pulses are feeble or absent, vascular imaging and vascular surgery consultation to assess the need for angioplasty/vascular intervention is needed to secure vessel potency and blood flow to the extremities. Nifedipine may be started in high dosages (30 mg four times a day) and in extreme situations, when digit or

limbs are at risk, an intravenous iloprost or epoprostenol infusion combined with anticoagulation (heparin, 5.000 UI twice daily) is preferable. A recent meta-analysis concluded that the use of iloprost in critical limb ischemia was efficacious in terms of pain relief, ulcer healing, and reduced need for amputations (33). These infusions are usually administered in a telemetry equipped wards under the care of cardiologists. Sympathetic block with anesthetics may also achieve a rapid vasodilatation. It is important to use effective analgesia, and local care of DUs with necrotic tissue debridement and infection control with appropriate antibiotics is crucial for full recovery. Therapeutic angiogenesis with autologous stem cells in patients lacking options for revascularization remains to be tested in future large-scale randomized trials (34).

Conclusions

The diagnosis of RP and categorization into pRP and sRP is very important and is largely a clinical challenge for the dermatologist. Laboratory and imaging investigations are driven by clinical suspicion of secondary causes or due to concerns for peripheral vascular disease, respectively. Non-pharmacological management such as avoidance of RP triggers, peripheral and core re-warming and use of protective clothing are vital. If RP is severe or if ulcers occur, pharmacotherapy may be recommended to control the attacks. In sRP pharmacological therapy is usually needed, CCBs being the first line of treatment (nifedipine or amlodipine most frequently used). If the attacks persist despite maximal doses of CCBs, then other medical therapies are recommended, and referral to a specialist in RP should be considered.

In conclusion, the approach to RP is a coordinated care with various specialists involved along with the primary care physician.

Abbreviations

RP: raynaud's phenomenon

pRP: primary raynaud's phenomenon

sRP: secondary raynaud's phenomenon

NC: nailfold capillaroscopy

DU: digital ulcer

CTD: connective tissue disease

SSc: systemic sclerosis

ANA: anti-nuclear antibodies

ACA: anti-centromere antibodies

Anti-Scl70: anti topoisomerase-I antibodies

UCTD: Undifferentiated CTD

SLE: systemic lupus erythematosus

RA: rheumatoid arthritis

DM: dermatomyositis

PM: polymyositis

SjS: Sjogren syndrome

RCS: Raynaud's Condition Score

MRA: Magnetic Resonance Angiography

CCBs: calcium channel blockers

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Table I: Classification of Raynaud's phenomenon (RP)

Primary RP	Secondary RP
Young women [< 30 years]	Patients aged >30 years
Attacks are symmetric and are of short duration	Attacks are asymmetric, extremely painful and prolonged
No tissue lesions (digital pitting scars, telangiectasia)	Tissue lesions seen
No complications (digital ulcers, necrosis/gangrene) on the extremities	Local complications common
Normal nailfold capillaroscopy	Abnormal nailfold capillaroscopy in the setting of CTD
Usually no suggestive features of CTD on clinical evaluation	Association with CTD is common
Autoantibodies negative	Autoantibodies could be positive when associated CTD

Table II: Causes of secondary RP

1. *Autoimmune/Connective tissue diseases*: Systemic Sclerosis, Systemic Lupus Erythematosus, dermatomyositis, polymyositis, Sjogren's syndrome, primary biliary cirrhosis, Rheumatoid Arthritis
2. *Arterial diseases*: thromboangiitis obliterans (Buerger's disease), Takayasu vasculitis, giant cell arteritis, brachiocephalic atherosclerosis.
3. *Mechanical*: vibration (white hand vibration syndrome), crutch pressure, thoracic outlet syndrome, scalenus anticus syndrome, cervical rib, carpal tunnel syndrome.
4. *Temperature*: frostbite
5. *Endocrine disorders*: carcinoid syndrome, pheochromocytoma, hypothyroidism
6. *Neoplasia*: ovarian carcinoma, angiocentric lymphoma.
7. *Rheological and coagulation disorders*: cryoglobulins, cryofibrinogenemia, cold agglutinins, paraproteinemia, plasmacytoma, polycythemia, microthromboembolism.
8. *Infections*: parvovirus B19 , helicobacter pylori , hepatitis C and B, mycoplasma (cold agglutinins).
9. *Medications* => see **table III**

Table III : Drugs inducing Raynaud's phenomenon

Drugs can induce RP mainly through 3 known mechanisms: enhanced vasoconstriction, endothelial damage or neurotoxicity and increased blood viscosity

Drug	**Mechanism**
β-blockers	Vasoconstriction via beta-adrenoreceptor blockade but still unclear.
Clonidine	α2 –adrenoreceptor agonist. In RP we already find a cold-amplified α2-mediated vasoconstriction, augmented by clonidine action. (α2 receptor are located on smooth muscle cells)
Ergot alkaloids	Vasoconstriction via 5HT2 receptors on blood vessels + α1adr, α2adr, and dopamine receptor agonists.
Dopamine agonists	Such as bromocriptine, share the same mechanism as ergot alkaloids at high doses.
Central stimulators of dopaminergic and noradrenergic system	Peripheral release of catecholamines i.e. methylphenidate and dextroamphetamine, atomoxetine, reboxetine; amphetamine-like drugs like phentermine
Cyclosporine	Unclear, maybe vasospastic effect and alteration in blood viscosity
Cocaine	α2-adrenoreceptor mediated vasoconstriction
Chemotherapies	3-6 months after starting. Drugs: bleomycin, vinca alkaloids, cisplatin mainly, less known for other therapies,
Vinyl Chloride	Occupational and/or environmental exposure
Interferons (IFNs)	IFNα>IFNβ>IFNγ, unclear, probably enhances vasoconstriction and increases blood viscosity.
Tyrosine Kinase Inhibitors	Unknown
Potentially RP inducers	**Few cases in literature**
Selective Serotonine Reuptake Inhibitors (SSRI)	Contradictory data in the literature, apparently it depends on variability in serotonin patterns
Sympathomimetics	i.e. ephedrine. Only 1 patient reported in literature
Sulfasalazine	Unknown mechanism
Amphotericin B	Unknown mechanism

Propofol	Unknown mechanism

Table IV: Physical characteristics of Raynaud's phenomenon, Erythromelalgia, Acral Cyanosis, and Livedo Reticularis

	Raynaud's phenomenon	Acral Cyanosis	Erythromelalgia	Livedo Reticularis
Classification	Primary / secondary	Primary / secondary	• Familial, (autosomal dominant) • Sporadic • Juvenile/adult	Primary / secondary
Phases of color change	Bi-triphasic/ white,blue,red	Monophasic / dark blue	Monohasic /erythematous	Macular, violaceous, netlike rings
Laterality	Primary-bilateral & symmetrical Secondary-mono/bilateral asymmetric	Mono/bilateral	Bilateral	Bilateral
Pain	++	Uncommon	++++	-
Limb	Hands, feet, nose, ears, tongue	Hands, feet	Feet (may extend to hand, ears and nose)	Upper and lower limbs
T°extremities	Cold	Cold	Hot	Cold
Precipitated by	Cold	Cold & lowering of the limb	Hot	Cold
Phase/duration	Paroxistic/lasts from minutes to hours	Chronic/ seasonal (amelioration in summer)	Intermittent/ may last from minutes to days	Primary:chronic Secondary- acute/ intermittent/chronic
hyperhydrosis	+	+++	Significant reduction	----
Modification of the phenomenon with the position of the limb	No change	Normalizes when limb is elevated	No change	No change
Complications	Digital Ulcers, gangrene, amputation	None	None	None in primary, in secondary possible necrosis

				and gangrene

Table V: Therapies for Raynaud phenomenon

Medication	Dose	Side-effects	In practice
Calcium channel blockers [CCB]			
Nifedipine	10 – 30 mg three times daily, oral	Flushing and hypotension, headache, tachycardia, dizziness, exacerbation of gastro-esophageal reflux	**First line medications** in RP. Also recommended when beta-blockers must be used for other co-morbidities
Nifedipine SR	30 – 120 mg daily, oral		
Amlodipine	5 – 20 mg daily, oral		
Prostanoid derivatives			
Iloprost	0.5 – 2 ng/kg/min for 3–5 days	Dose-dependent: peripheral vasodilation (hypotension, tachycardia, headache, flush) or bowel activation (diarrhea, nausea) The use of iloprost in patients with myocardial ischemia and congestive heart failure should be carefully monitored for a potential of a coronary steal syndrome or pulmonary edema	Iloprost not available in USA, mainly used in Europe for the treatment of RP-SSc and critical limb ischemia Iloprost and alprostadil are both of benefit RP- SSc-in practice; ease of handling and the lower price favor Alprostadil. No evidence of effect of Beraprost on the frequency, severity or duration of RP attacks Repeated long-lasting epoprostenol infusion reduce RP but effect lost after 1 week.
Alprostadil	every 6–8 weeks, intravenous		
Beraprost			
Epoprostenol	2 ng/kg/min, with increase of 2 ng/kg/min every 30 minutes to the individually tolerated maximal dose of 8 ng/kg/min, intravenous		
Phosphodiesterase-5 inhibitors (PDE5i)			
Sildenafil	Total daily dose 100 mg	Headache, cutaneous flushing, dizziness, nasal congestion	Reduces frequency, duration and severity of the attacks.
Tadalafil	20 mg at alternate days		Improvement of RP symptoms and ulcer healing
Vardenafil			Reduces severity of the

			attacks and improves Raynaud's Condition Score
Endothelin receptor antagonists (ERA)			
Bosentan			Did not reduce frequency duration and pain of the attacks but prevented recurrence of DUs.
Drugs interfering with intracellular calcium activity			
Minoxidil	topical minoxidil 5% solution		Not effective in improving baseline digital blood flow or cold tolerance in RP
Sympathetic blockade			
Prazosin	1 – 5 mg two times daily, oral	Dizziness, hypotension and syncope	Modest effect on RP. Reduction of the attacks and DUs healing.
Botulinum toxin – A	Dose dependent vasodilation with 10-100 units injections		Favorable results in many studies despite limitations. Improving of pain, severity, and reduction of DUs frequency
Angiotensin – II receptor blocker			
Losartan	25 – 100 mg daily, oral	Dizziness, hypotension	One trial showed benefit in SSc patients with RP but seldom employed in practice
Serotonin re-uptake inhibitor			
Fluoxetine	20 – 40 mg daily, oral	Apathy, lethargy and impaired concentration	One trial showed benefit in SSc patients with RP but seldom employed in practice
Phosphodiesterase – 3 inhibitor			
Pentoxifylline	400 – 1200 mg	Dizziness, hypotension,	Has anti-platelet aggregation

	daily, oral	nausea, diarrhea	property
Topical nitroglycerine			
Nitroglycerine patches	0,2 mg/h (slow release)	Headache	Reduction of number and severity of the attacks
0,9% nitroglycerine gel			Improvement in frequency and duration of the attacks and of RPS
Combination therapy: PDE5i + ERA			
Bosentan + sildenafil		Reduction of late and active capillaroscopic patterns, improvement of the RP	

Figure 1: Asymmetric Raynaud's phenomenon in a 28-year-old woman (blanching phase)

Figure 2: a stepwise approach to RP evaluation
Abbreviations: NC= nail fold capillaroscopy, DU = digital ulcers, SSc= systemic sclerosis, SLE = systemic lupus erythematosus, EMG= electromyography, NCV = Nerve Conduction Velocity, TSH = thyroid stimulating hormone, TPO = thyroperoxidase, TG = thyroglobulin, HCV= Hepatitis C Virus, BUN = blood urea nitrogen

Figure 3: Raynaud phenomenon in a 28-year-old woman with antinuclear and anti-centromere antibodies positivity, active capillaroscopy pattern with one micro-hemorrhage (insert a). She was diagnosed with very early systemic sclerosis. The digital swelling worsened with the development of a digital ulcer in the third finger (insert b).

Figure 4: Raynaud phenomenon in a 57-year-old woman with puffy fingers. In the two inserts, capillaroscopy shows micro hemorrhages (a) and mega capillaries (b). The patient had antinuclear and anti-centromere antibodies without any skin fibrosis. A diagnosis of very early systemic sclerosis was made.

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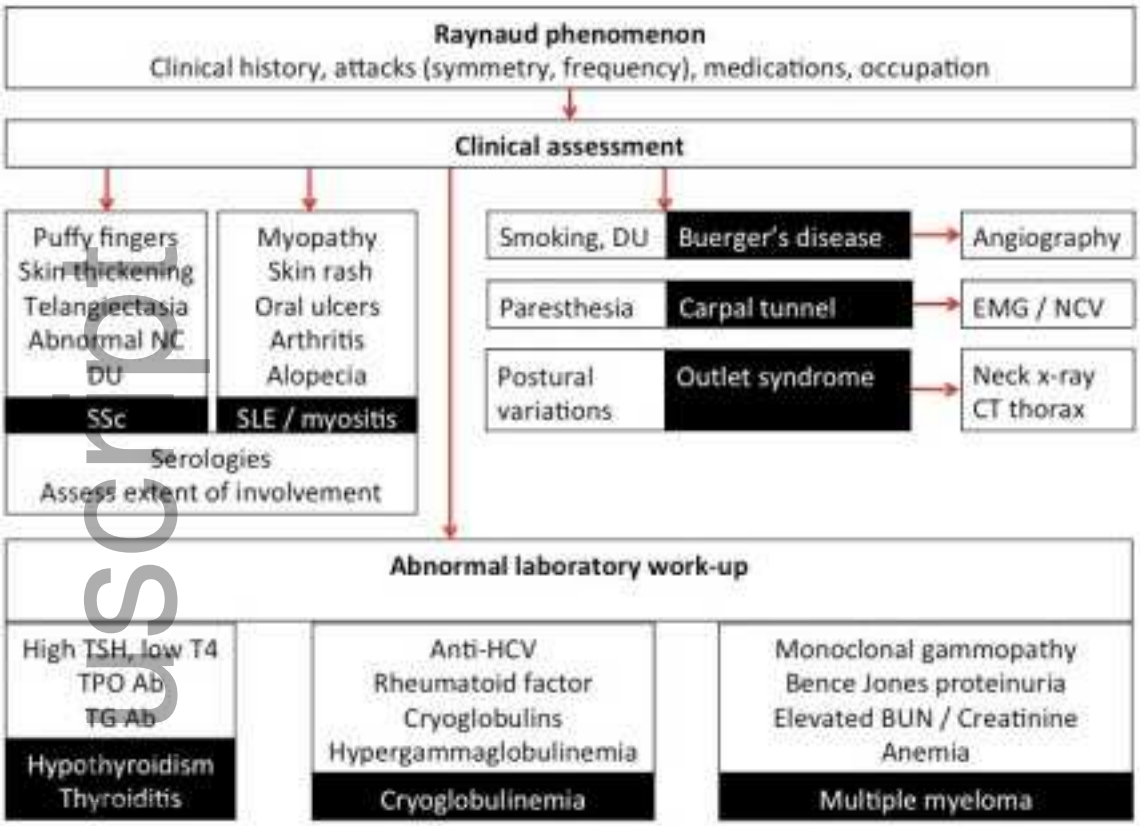

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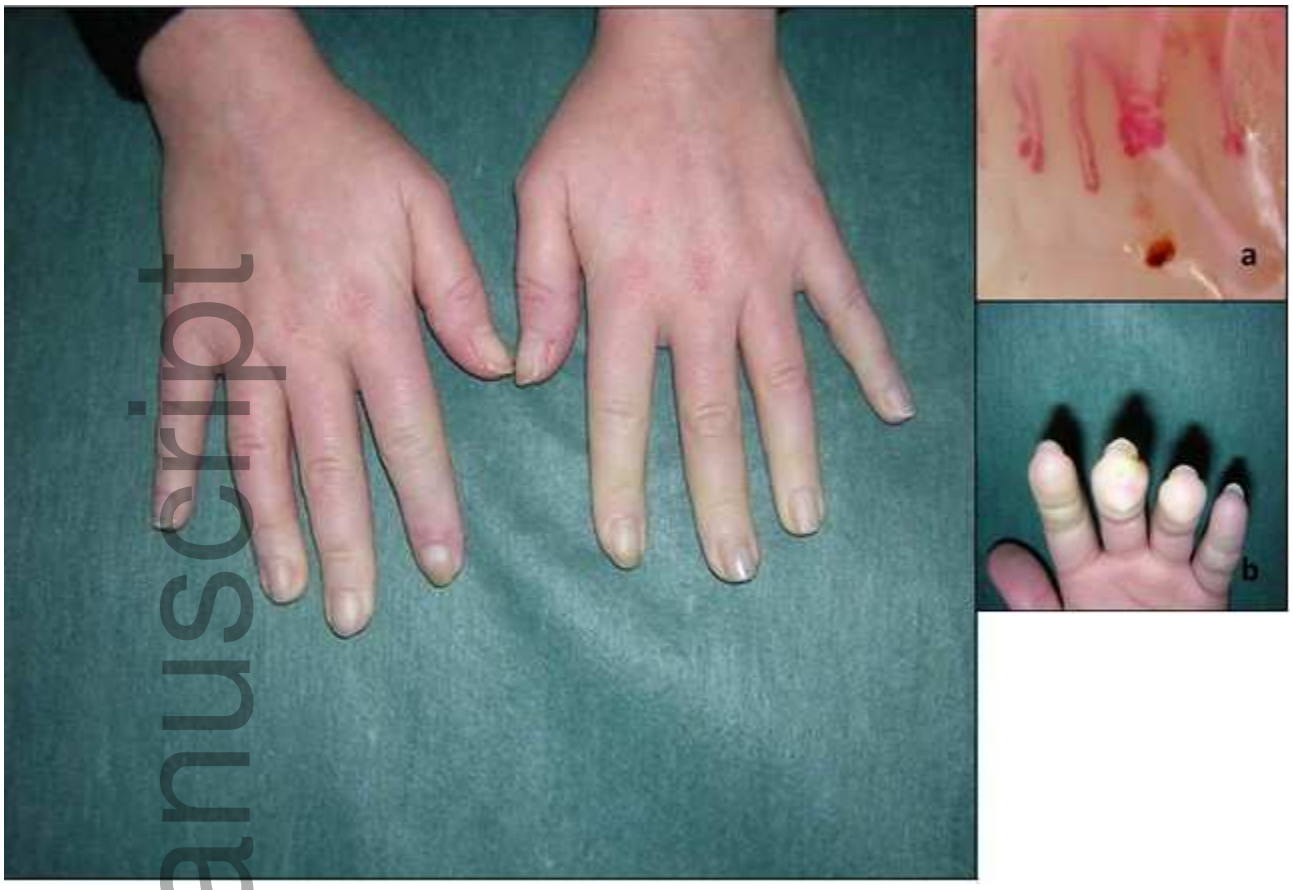

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