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Evaluation of the Patient with Recent Onset of Raynaud Symptoms

Thomas A. Medsger Jr., MD
Professor of Medicine, Division of Rheumatology and Clinical Immunology

Robyn T. Domsic, MD, MPH
Assistant Professor of Medicine, Division of Rheumatology and Clinical Immunology

University of Pittsburgh
School of Medicine
Division of Rheumatology
and Clinical Immunology
Pittsburgh, Pennsylvania

Address correspondence to:

UPMC Rheumatology and
Clinical Immunology
S700 Biomedical Science Tower
3500 Terrace St.
Pittsburgh, PA 15261
Telephone: 412-383-8765
Fax: 412-383-8753
tam8@pitt.edu
rtd4@pitt.edu

Raynaud disease (or primary Raynaud phenomenon) is defined as repeated episodes of bilateral color changes at the tips of the fingers upon exposure to cold or emotional stress. The toes may also be affected; this occurs less frequently and less severely than in the fingers. The condition is due to transient exaggerated arteriolar vasoconstriction without structural abnormalities of arteries, arterioles or capillaries. White (blanching) is the most characteristic and reliable color observed, followed by blue/grey (cyanosis) and red (reactive erythema) during rewarming. Individual "attacks" last from 5-30 minutes and are most often accompanied by some neuritic symptoms (numbness, tingling, pain) due to ischemia of digital sensory nerves.

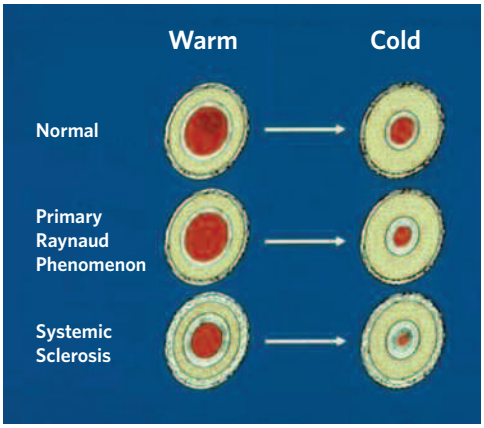


Figure 1. Diagram showing normal and abnormal blood vessel structure and response to cold exposure. In systemic sclerosis there is subintimal thickening, medial hypertrophy, and periadventitial fibrosis.

Because these episodes are self-limited in duration, there should be no permanent tissue loss, such as digital tip ulceration, gangrene or residual digital tip "pitting" scars, which signify loss of subcutaneous fingertip tissue. If such trophic changes are present, the physician should conclude that the patient does not have uncomplicated Raynaud disease, but instead has Raynaud phenomenon due to an underlying connective tissue disease (CTD) such as systemic sclerosis (scleroderma or SSc), systemic lupus erythematosus, Sjogren syndrome, polymyositis-dermatomyositis, or an undifferentiated CTD. When digital tip tissue loss is present, there is structural damage of small blood vessels with endothelial cell dysfunction, subintimal thickening, and vascular smooth muscle proliferation leading to lumenal narrowing, in addition to vasospasm *(Figure 1)*.

Raynaud disease is relatively common in the adult population (5-10% females and 3-5% males), while Raynaud phenomenon due to CTD is much less frequent. This distinction is important because CTDs can result in serious or life-threatening internal organ complications. The question that the managing physician must answer is, "Does my patient have Raynaud disease or Raynaud phenomenon?" The standard approach is to gain as much information as possible from history, physical examination, laboratory tests, and special procedures.

Table 1 shows historical features that may be helpful in distinguishing Raynaud disease from Raynaud phenomenon. Raynaud disease is associated with other common conditions in which there is an exaggerated response to physical and/or emotional stimuli, such as migraine headache, fibromyalgia, and irritable bowel syndrome. The other listed symptoms are much more frequently encountered in CTDs than in the general population, and often provide important clues to an underlying CTD.

TABLE 1: Historical Features Helpful in Distinguishing Raynaud Disease (RD) from Raynaud Phenomenon Due to Connective Tissue Disease (RP-CTD)

Features	*RD*	*RP-CTD*	*Associated Connective Tissue Disease*
migraine headache	+	±	APL
fibromyalgia	+	0	
irritable bowel syndrome	+	0	
depression	+	0	
arthralgias/arthritis	0	+	SLE, SS
pleurisy	0	+	SLE
dry eyes/dry mouth	0	+	SS
proximal muscle weakness	0	+	PM/DM
rash	0	+	DM, SLE
swollen fingers	0	+	SSc
heartburn	0	+	SSc
distal dysphagia for solid foods	0	+	SSc
proximal dysphagia for liquids	0	+	PM/DM

SLE= systemic lupus erythematosus; SS=Sjogren syndrome; SSc=systemic sclerosis; PM/DM= polymyositis/dermatomyositis; APL = antiphospholipid antibody syndrome

TABLE 2: Physical Examination Findings Suggestive of CTD

Findings	*CTD*
puffy fingers	SSc
sclerodactyly (thickening of digital skin)	SSc
digital pitting scars, ulcers or gangrene	SSc
rash of DM	DM
rash of lupus	SLE
glossitis	SS
pleural or pericardial friction rub	SLE
proximal muscle weakness	PM/DM
grossly abnormal (dilated) nailfold capillaries	SSc, others
subcutaneous/intracutaneous calcinosis	SSc
digital/facial/lip telangiectasias	SSc
palpable tendon/bursal friction rubs	SSc
polyarthritis	SLE, others

SLE= systemic lupus erythematosus; SS=Sjogren syndrome; SSc=systemic sclerosis; PM/DM= polymyositis-dermatomyositis

Physical findings are often good indicators of CTD *(see Table 2)*. Additionally, laboratory findings are useful in helping to distinguish Raynaud disease from Raynaud phenomenon. Laboratory results that show abnormal acute phase reactants, hematologic, immunologic, mucocutaneous, muscular, pulmonary, cardiac, or renal dysfunction may indicate Raynaud phenomenon *(see Table 3 on page 4)*. None of these abnormalities is expected to be present in patients with Raynaud disease.

Given a patient with Raynaud disease on the basis of history and physical examination at the time of first evaluation, which laboratory findings most accurately predict the future development of a CTD? Several large, long-term follow-up studies of patients presenting with Raynaud symptoms have shown that a positive antinuclear antibody (ANA) test and abnormal nailfold capillaries are the two most important predictive objective findings. After 15 years of follow-up, 85% of Raynaud disease

patients with either a positive ANA or abnormal nailfold capillaries developed systemic sclerosis.[1]

Although some Raynaud patients have grossly visible nailfold dilatation, the best method to detect these changes is with magnification using a high-quality, hand-held magnifier. The abnormalities most frequently detected are dilated capillaries, capillary "dropout," and pericapillary hemorrhage.[2-6] Various patterns of change have been felt to be more characteristic of certain connective tissue

TABLE 3. Laboratory and Special Test Findings Distinguishing RD from RP-CTD

Findings	*RD*	*RP-CTD*	*Associated CTD*
anemia	0	±	all CTDs
leukopenia	0	+	SLE, SS
thrombocytopenia	0	+	SLE
elevated ESR/CRP	0	+	all CTDs
acute renal failure	0	+	SLE, SSc
elevated CPK/aldolase	0	+	PM/DM
positive ANA	0	+	all CTDs
anti-SSA/SSB antibody	0	+	SS
anti-RNA polymerase III antibody	0	+	SSc
anti-centromere antibody	0	+	SSc
anti-Scl 70 antibody	0	+	SSc
anti-Jo1 antibody	0	+	PM/DM
anti-U1RNP antibody	0	+	SSc, SLE, PM/DM
abnormal nailfold capillaries	0	+	all CTDs
abnormal peripheral arterial Dopplers or arteriogram	0	+	all CTDs
distal esophageal hypomotility	0	+	SSc
low C3 and C4 complement levels	0	+	SLE, SS
low C4 complement level only	0	+	SS
abnormal sialogram or lip biopsy	0	+	SS
pulmonary fibrosis	0	+	SSc, PM/DM
microscopic hematuria/proteinuria	0	+	SLE, SSc
abnormal pulmonary function tests	0	+	SSc, PM/DM
pulmonary arterial hypertension	0	+	SSc
cardiomyopathy/pericardial effusion	0	+	SSc, SLE

SLE= systemic lupus erythematosus; SS=Sjogren syndrome; SSc=systemic sclerosis; PM/DM= polymyositis-dermatomyositis

disorders, but the important distinction to be made is whether any of the above three alterations are "present" or "absent" *(Figure 2)*.

With regard to ANA testing, methodology is important. Physicians should be sure that the laboratory performing the ANA testing uses indirect immunofluorescence (IIF). Results will be given as negative or positive at a particular titer, e.g. 1:80, 1:160, 1:320, etc. One to 80 is a borderline positive and 1:160 or greater a definite positive test. Beware that newer tests are done by an enzyme-linked immunosorbent assay (ELISA) or "bead" method, with results reported as numbers, such as 2.2 units (normal <1.0). These tests can give false negative results, as some CTD associated autoantibodies are not identified by this assay. For example, only four of the nine SSc-associated antibodies are detectable using most of these methods.

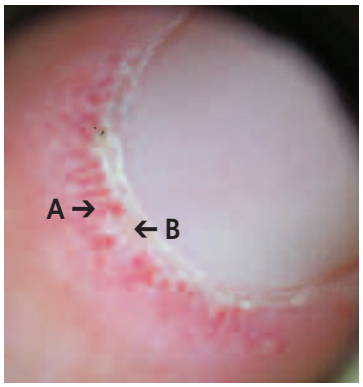


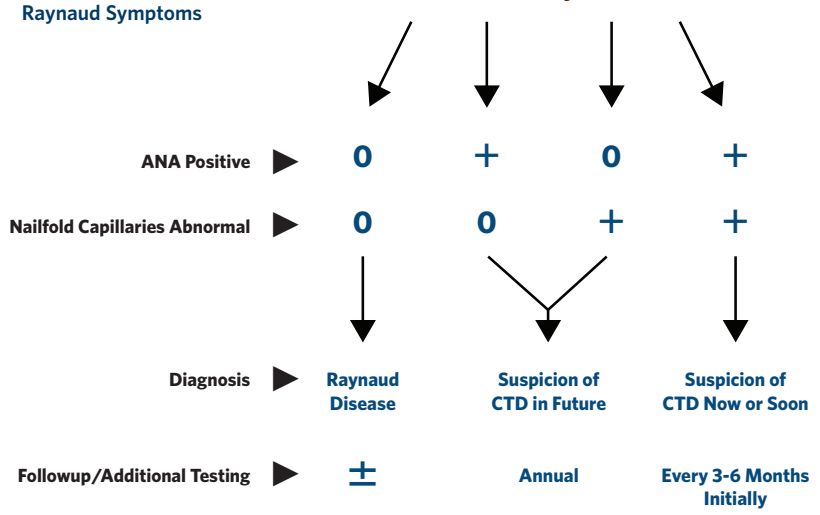
Figure 2. Photo showing nailfold capillary dilatation (A) and dropout (B). *(courtesy of Joseph C. English III, MD and Arthur Huen, MD, PhD, Department of Dermatology, University of Pittsburgh School of Medicine)*

Beyond a positive ANA, there are now many specific antibodies that can be detected and that have strong disease correlations. Unfortunately, commercial laboratories rarely test for antibodies such as anti-U3RNP, anti-Ku, anti-Th/To and anti-U11U12RNP for systemic sclerosis and several anti-synthetase antibodies found in the inflammatory myopathies, e.g. anti-PL12, anti-PL7, anti-EJ, etc. For patients referred to UPMC for evaluation of Raynaud symptoms who have a positive ANA, the Division of Rheumatology and Clinical Immunology's Immunoassay Core Laboratory can perform additional autoantibody testing if commercial laboratory tests are unavailable or the results conflicting or inconclusive. These supplemental studies are completed as part of our ongoing SSc and Raynaud disease observational registries. They will be done at no cost to the patient or his/her medical insurance carrier.

For more information on the clinical associations of these systemic sclerosis-related antibodies, refer to journal articles that have been published by UPMC faculty and staff members.[7-14]

If a patient has either a positive ANA by IIF or abnormal nailfold capillaries, the physician's suspicion should be increased that one or more of the abnormalities listed in *Tables 1, 2, and 3* will occur in the future. It is most appropriate to follow these patients closely, rather than advising them that the diagnosis is Raynaud disease and of "little concern" *(see Figure 3 diagram)*.

Figure 3. Schematic Summary of the Proper Evaluation of a Patient with New Onset Raynaud Symptoms



Case Vignette

PD is a 35-year-old woman who noted the onset of typical Raynaud symptoms in the winter of 2007-2008. She was a one-pack-a-day cigarette smoker. The Raynaud symptoms improved during the summer of 2008 but recurred in the fall of 2008. Her fingers appeared somewhat swollen, particularly in the mornings. She also complained of recent heartburn. She saw her primary care physician, who did a CBC, differential count, platelet count and complete metabolic profile, all of which were normal. He referred her to a rheumatologist, who noted puffy fingers only. Capillary microscopy was not done. The ANA was ordered and was negative by an ELISA method. The rheumatologist advised the patient by telephone, "You have Raynaud disease. This is a frequent condition. Use common sense regarding cold exposure and discontinue smoking. Make sure not to eat spicy foods and take Tums for your heartburn if needed. Nothing serious is likely to happen. See me again if you have any problems."

The patient followed instructions and was able to stop smoking. However, Raynaud symptoms persisted and she developed a small, slightly painful right index fingertip ulcer. Her PCP prescribed an antibiotic ointment to apply to the fingertip. In April 2009, the patient's finger skin became hard/thick and she noted inflammatory arthalgias affecting the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints bilaterally with prominent morning stiffness. Her knees and ankles were "squeaky" with motion. She had generalized pruritus and mild fatigue. She requested an appointment to see the rheumatologist again, but could not be scheduled until July 2009. In May 2009, she developed headaches on awakening in the morning, which became increasingly severe. One evening in late May 2009, she noted shortness of breath, which alarmed her. She went to her local hospital emergency room where her blood pressure was reported to be 220/110 mmHg and she was admitted for evaluation of accelerated arterial hypertension.

During hospitalization, the patient was found to have acute renal failure with a serum creatinine of 4.2 mg/dL and microangiopathic hemolytic anemia with thrombocytopenia. She had skin thickness affecting the fingers, hands, forearms and anterior chest, bilateral anterior tibial tendon friction rubs, finger joint contractures and digital pitting scars. The ANA was positive 1:640 by IIF and the anti-RNA polymerase III antibody test was strongly positive. The diagnosis of "scleroderma renal crisis" was made. Despite improvement in blood pressure, which required four drugs including an ACE inhibitor, she became dialysis-dependent.

This case illustrates the importance of paying attention to clues provided by the patient history and physical examination.

Case Vignette Outcome

This case illustrates the importance of paying attention to clues during the patient history (heartburn) and physical examination (puffy fingers). These findings should increase suspicion of evolution of Raynaud disease to systemic sclerosis. It also demonstrates that performing a reliable ANA test and doing capillary microscopy might have altered the outcome. In retrospect, the better working diagnosis would have been "possible systemic sclerosis." The ANA was likely to be positive at the time of the first rheumatologist visit if performed using indirect immunofluorescence. The anti-RNA polymerase III antibody test also would have been positive. An esophagram would probably have confirmed distal esophageal hypomotility.

In our clinic we would have recommended a return visit in 3-4 months. If there was clinical and serologic confirmation of scleroderma the patient would have been advised to take her blood pressure weekly and to report any sudden increase of 30 or more points (either systolic or diastolic). If hypertension had been identified early, it is possible that it could have been stabilized, with acute renal failure being aborted, or at least its progression minimized.

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