The Temporal Relationship of Raynaud's Phenomenon and Features of Connective Tissue Disease in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** In a prospective cohort study we examined the relationship between Raynaud's phenomenon (RP) onset and other connective tissue disease (CTD) characteristics in rheumatoid arthritis (RA) to determine if RP is predictive of RA severity and associated with other CTD signs, and if late onset RP in RA has an effect on prognosis compared to other patients with RA.

Methods. Using a standardized assessment, data were collected on 328 subjects with RA [mean age 60.3 ± 0.7; 77% women; 76% erosions, 75% positive rheumatoid factor (RF)] seen at one London, Ontario, rheumatology clinic. The data included RA disease duration; presence and duration of RP; presence of nodules, joint damage, telangiectasia, and sclerodactyly; and RF status (+/–), RF value, antinuclear antibodies, and E-nuclear antibodies.

Results. The mean RA disease duration was 12 ± 0.6 years. Seventy-one (22%) had RP and the mean RP duration was 9.2 ± 1.5 years. Patients presented with RP a mean of 3.8 ± 1.4 years after the diagnosis of RA. RP status was positively associated with the presence of sclerodactyly ($p < 0.001$), but not nodules or erosions. Higher RF values were associated with longer RA disease duration ($p < 0.002$) and longer RP duration ($p < 0.01$).

Conclusion. Idiopathic RP may have a different clinical effect on RA than secondary RP; the latter is correlated with more severe RA. Sclerodactyly is associated with erosive arthritis and RP in RA. Higher RF values were indicative of increased RA and RP duration. (First Release Oct 1 2008; J Rheumatol 2008;35:2329–33; doi:10.3899/jrheum.071025)

Key Indexing Terms:
RAYNAUD'S PHENOMENON RHEUMATOID ARTHRITIS
CONNECTIVE TISSUE DISEASE PREVALENCE SCLERODACTYLY

Rheumatoid arthritis (RA) is a heterogeneous autoimmune inflammatory arthritis in which symptoms may vary from mild to severe. More severe RA is characterized by increased bone erosions, rheumatoid nodules, and positive rheumatoid factor (RF)[1]. Raynaud's phenomenon (RP) is a condition in which the digits exhibit pallor with exposure to cold, and cyanosis and/or rubor upon rewarming. RP often occurs in connective tissue diseases, such as scleroderma (systemic sclerosis, SSc), but less frequently in RA. The reported prevalence of RP in RA in the literature has been variable, ranging from < 3% to > 20%[2-4]. Discrepancies between studies may be partly due to definitions of RP used[4,5]. The significance of RP in RA is unclear. Saraux, *et al* examined the association of RP in RA with other clinical features, but temporal relationships were not assessed[4]. This group reported a 17% prevalence of RP in RA, but no significant correlations between RP and demographic, clinical, or radiological characteristics were reported. In one study, RP in RA was associated with increased joint damage[6]. We wanted to characterize the temporal relationship between RA and RP, the frequency of RP in our RA population, and its clinical correlations such as sclerodactyly, large telangiectasia and RA severity.

MATERIALS AND METHODS

Data were collected on a prospective cross-sectional cohort of patients with RA (n = 328; mean age 60.3 ± 0.7; 77% women; 76% erosions) who met the American College of Rheumatology (ACR) criteria for RA[7] and had been seen in one rheumatology practice in London, Ontario, over the 6-month study period. Overlaps with systemic lupus erythematosus (SLE) or scleroderma were excluded. The standardized assessment form included disease duration; presence of rheumatoid nodules, damage (defined as subluxations, joint surgery for RA, and/or known erosive disease on previous radiographs), telangiectasia, sclerodactyly, and dilated nailbed capillaries; presence and duration of RP (RP definition demanded digital pallor and at least 1 of rubor or cyanosis by history); and RF (+/–), RF value, and antinuclear antibody (ANA) and E-nuclear antibody (ENA) status if available. A standardized examination included an assessment of rheumatoid nodules; telangiectasia for presence, size (large: yes/no), and location (facial/other);

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and presence and location of sclerodactyly. All patients were seen by the same 2 observers (JEP and JA-B) and sclerodactyly was defined as tight skin and the inability to pinch skin, and was characterized by location proximal to the metacarpophalangeals (MCP), up to the MCP or distal to the proximal interphalangeal joints (PIP). Patients were also assessed for the number of dilated nailbed capillaries. Charts were reviewed for erosions, radiographs, laboratories, RF, ANA, and ENA. Data were analyzed for statistical significance ($p < 0.05$); comparisons were made between patients with and without RP using t tests, chi-squared analysis, and confidence intervals (CI) where appropriate.

RESULTS

Three hundred twenty-eight patients with RA seen serially in 1 clinic were identified, of whom 71 (22%) also had RP. All patients met ACR criteria for RA. Five patients with RA/SLE (n = 3) and RA/scleroderma (n = 2) overlaps were excluded, as well as 1 patient with ambiguous RP status, but those with secondary Sjögren's syndrome were not excluded. The patients did not differ by sex (78% women with RP and 77% women without RP) or age (60.2 ± 1.5 yrs in patients with RP and 60.3 ± 0.8 yrs in patients without RP). The mean ± standard error of the mean (SEM) RA disease duration was 12.4 ± 0.6 years. Duration of RP was 9.2 ± 1.5 years and the mean age of onset of RP was 50.7 ± 2.0 years. Table 1 shows demographic and disease characteristics of RA patients with and without RP.

RF was positive in 75% of all patients with RA and the mean (SEM) RF value was 247 ± 30. Seropositivity for RF was more prevalent in men (85% vs 71%; $p < 0.03$). As expected, a positive RF was associated with damage ($p < 0.0005$) and longer RA disease duration ($p < 0.02$). Patients with a higher positive RF were more likely to have longer RA disease duration ($p < 0.002$) and longer RP duration ($p < 0.01$). The serology (RF and ANA, where available) was not associated with RP. No associations between ENA were found, but only 16% of all patients had available ENA data.

Seventy-six percent of patients were known to have joint damage and 33% had nodules (ever). Damage was associated with sclerodactyly ($p < 0.04$) and was more likely to be found in patients who developed RP after RA ($p < 0.003$). A significant association was found between sclerodactyly and RP ($p < 0.001$). All sclerodactyly was only distal to the PIP. Of the 328 patients, 29 (42%) out of the 71 patients with RP presented with sclerodactyly compared to 55 (21%) patients without RP (RR 2.54; 95% CI 1.45–4.44). An increased disease duration was seen in patients who presented with RP before RA ($p < 0.002$).

Only 7 patients (2.1%) had onset of RP more than 3.8 years prior to the onset of RA (similar to the prevalence of primary RP). Thirty-one patients (9.4%) had onset of RP

Table 1. Disease characteristics in patients with rheumatoid arthritis (RA) with and without Raynaud's phenomenon (RP). Data are presented as percentage of patients and for each symptom or as mean (SEM) where applicable.

	RA	Raynaud's, n (%)	No Raynaud's, n (%)	OR:RP vs No RP	95% CI	p, RP vs No RP
No. of patients	328	71 (21.5)	257 (78.5)	—	—	—
Age (SEM), yrs	60.3 ± 0.7	60.2 ± 1.5	60.3 ± 0.8	—	—	1.0
Disease Duration (SEM), yrs	12.4 ± 0.6	13.0 ± 1.3	12.3 ± 0.7	—	—	0.5
Female, %	76.8 (n = 251)	77.8 (n = 56)	77.1 (n = 202)	1.0	0.6–2.0	0.9
Yrs RP before RA (SEM)	—	3.8 ± 1.4	—	—	—	—
Mean RP duration, yrs	—	9.2 ± 1.5	—	—	—	—
Mean age onset of RP, yrs	—	50.7 ± 2.0	—	—	—	—
RF (positive), %	75.0 (n = 168)	76.5 (n = 39)	71.7 (n = 129)	1.3	0.6–2.7	0.8
Nodules (positive), %	29.9 (n = 95)	31.0 (n = 22)	29.5 (n = 753)	1.2	0.7–2.2	0.3
Joint damage, %	76.0 (n = 192)	55.1 (n = 38)	61.8 (n = 157)	1.0	0.5–2.1	0.3
Telangiectasia (positive), %	18.6 (n = 60)	22.9 (n = 16)	17.4 (n = 45)	1.4	0.7–2.7	0.3
Sclerodactyly (positive), %	26.7 (n = 87)	41.7 (n = 29)	21.4 (n = 55)	2.7	1.5–4.6	0.001
Nailbed capillaries, %	1.9 (n = 6)	0 (n = 0)	2.3 (n = 6)	—	—	—
Mean no. nailbed capillaries	2.3 ± 0.5	0	2.3 ± 0.5	—	—	0.3
Mean RF value (SEM)	247 ± 30	285 ± 77	234 ± 30	—	—	0.5
ANA, %*	34.8 (n = 47)	38.2 (n = 13)	33.3 (n = 34)	1.2	0.6–2.8	0.6
ENA, %*	5.5 (n = 3)	6.3 (n = 1)	5.1 (n = 2)	1.2	0.1–14.6	0.9

* Percentages were small for ANA and ENA as there were missing data. SEM: standard error of the mean; RF: rheumatoid factor; ANA: antinuclear antibodies; ENA: E-nuclear antibodies.

within 3.8 years of the onset of RA and 23 (7%) had onset of RP more than 3.8 years after the onset of RA. In the 71 patients with RP, the 3 categories correspond to 9.8%, 43.7%, and 32.4%. Further analysis using Mantel-Haenszel test showed that the latter subgroup (later-onset RP) had more erosions (p = 0.01; Table 2), although this was not significant when correcting for disease duration.

Overall, 18.6% of the patients with RA had telangiectasia. Of those patients, 60% had developed large telangiectasia and 16% had facial telangiectasia. No association was found between RP and telangiectasia. Only 2% of patients had dilated nailbed capillaries.

Figure 1 shows the hand of a patient with longstanding seropositive nodular erosive RA with sclerodactyly and new-onset RP and some nailfold dilated capillaries.

DISCUSSION

We found that RP occurs in 22% of RA, which is on the high end of other case series[2-4]. Overall, we did not find that RP was associated with erosive RA, but observed that later onset of RP (after RA) was associated with more damage. It is difficult to understand why this link would occur, as the cytokines in RP seem different from those in erosions, but there may have been confounding disease duration[8,9]. Indeed, frequency of joint damage was not different between RP and no-RP groups, and when correcting for disease duration as a confounder the relationship between RP and erosions is no longer significant (p = 0.57). RP may have occurred in some as primary (yrs prior to RA, onset at a young age) and in many as secondary (through the association with RA). Primary RP is rare in age > 40 years, which is well before the median onset of RA in our patients. If RP started many years prior to RA and especially at a young age (childhood to 20s) it may have been primary, but this is only a hypothesis. RA associated with RP may have a worse prognosis, but this could also be due to removing overlaps (but only 6 patients were excluded: 3 with RA/SLE, 2 with RA/scleroderma, and 1 with an ambiguous case of RP).

The sclerodactyly could be from mild distal flexor tenosynovitis, glycosylation/citrullination of connective tissues, or repeated ischemia from RP. However, the sclerodactyly we found was not classic for scleroderma (all cases were at, or distal to, PIP joints) and could be related to older age, as it is often seen in older patients without disease. We looked for large SSc or connective tissue disease (CTD)-like telangiectasia in those with RP (Table 2), where they were uncommon, and indeed, all telangiectasia (large, CTD-like, and multiple) were not common in RA overall or in the RP and no-RP groups (Table 1). None of the patients had a history of digital ulcers and the RP was usually mild.

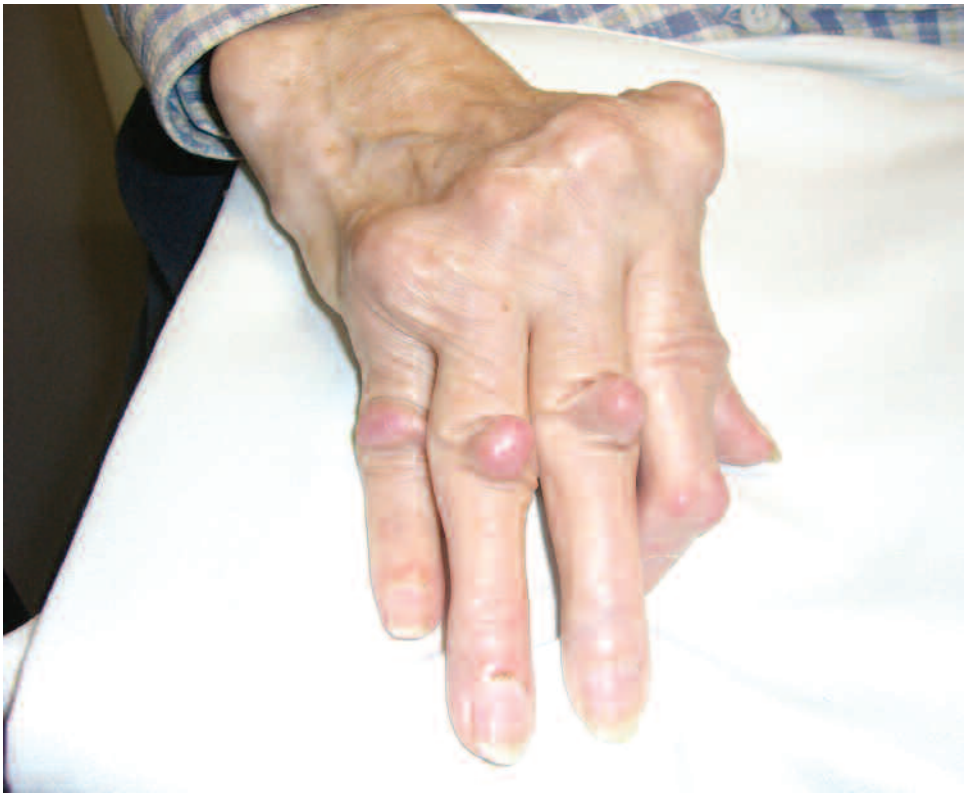
Several researchers have indicated that subjects with RA presenting concurrent RP should be considered special cases[1-3], and that RP in RA is not an early feature. Grassi, *et al*[3] also found a low occurrence of capillary damage, as seen in our study. RP is often associated with nonerosive disease in Sjögren's syndrome and MCTD[10-13].

Table 2. Associations between RP onset and RA disease manifestations. If disease onset of RP was unknown, patients were excluded (n = 10).

RA Manifestations	Subject with Onset of RP > 3.8 yrs Prior to Onset of RA, n = 7	Subjects with Onset of RP within 3.8 yrs of Onset of RA, n = 31	Subjects with Onset of RP > 3.8 yrs After Onset of RA, n = 23	p
Joint damage, %	14.3 (n = 1)	39.3 (n = 11)	78.3 (n = 18)	0.01†
Nodules, %	0 (n = 0)	29.0 (n = 9)	40.9 (n = 9)	0.1
Telangiectasia, %	33.3 (n = 2)	25.8 (n = 8)	22.7 (n = 5)	0.9
Large facial telangiectasia, %	20	13	9	1.0
Dilated nailfold capillaries, %	0	0	0	—
Sclerodactyly, %	28.6 (n = 2)	38.7 (n = 12)	39.1 (n = 9)	0.9
Rheumatoid factor (RF)-positive, %	66.7 (n = 4)	84.0 (n = 21)	71.4 (n = 10)	0.3
RF value, mean ± SEM	422 ± 287	205 ± 90	422 + 225	0.5
Positive ANA*, %	57.1 (4/7)	31.3 (5/16)	42.9 (3/7)	0.5
Positive ENA*, %	50.0 (1/2)	0 (0/9)	0 (0/4)	0.2
RA disease duration, mean ± SEM	9 ± 3.7	11 ± 2.2	17 ± 1.8	0.1

* ANA and ENA values were not available for most patients. Fractions indicate patients testing positive for the antibody out of the total patients tested in that category. P values were obtained by chi-squared analyses and mean ± SEM RF values by 1-way ANOVA. † This is not significant when corrected for disease duration (p = 0.57). RP: Raynaud's phenomenon; RA: rheumatoid arthritis; ANA: antinuclear antibodies; ENA: E-nuclear antibodies; SEM: standard error of the mean.

A



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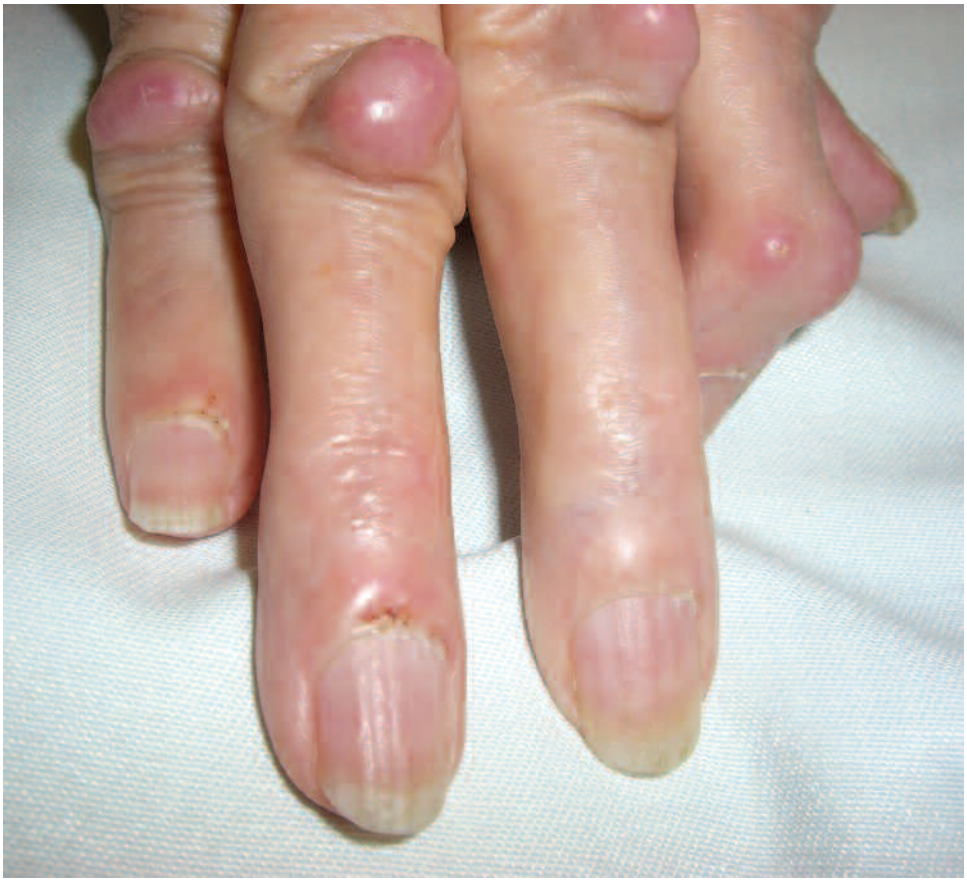

Figure 1. A. A patient with longstanding seropositive nodular erosive RA with sclerodactyly and new-onset RP. B. A closer view of the same patient.

A Swedish group reported that women with pronounced RP had a history of recurrent muscle/joint pain ($p < 0.05$); however, laboratory tests did not confirm a diagnosis of RA[14]. We did not find RP to be more prevalent among men, as Grassi, *et al*[3] observed, although we did find men to have an increased rate of RF seropositivity compared to women ($p < 0.03$).

Wagner, *et al* reported that in a study of patients with RA ($n = 94$), 11 subjects had RP, 10 of whom also had an expanded $CD4+CD28^{null}$ T cell compartment ($p < 0.005$)[15]. Underlying genetic factors may contribute to earlier RP in subjects prone to more severe RA[16]. In our study, ANA and ENA laboratory tests were frequently not available and weak associations may have been missed. Future studies could include assessment of vasculitis in our cohort, assessment of CD4T cells, ethnicity studies to assess differences in prevalence of RP in RA and whether the relationship between erosive arthritis and early RP observed here differs among ethnic groups, and evaluation of cumulated corticosteroid treatment, as that could modify skin atrophy.

RP is present in 22% of RA cases. Idiopathic RP may have a different clinical influence on RA than secondary RP. It is found, as expected, at a low prevalence (2.1%), which is similar to the general population and not seemingly associated with prognosis of RA. Secondary RP may be associated with more erosive arthritis. Secondary RP may be bimodal, with onset around RA versus onset in long-established RA (worse prognosis, but it may be confounded by RA disease duration). Sclerodactyly is also associated with RP and more erosive RA. Patients with higher RF values have increased RA disease duration and RP duration. There may be different subsets of patients with RP and RA: (1) RP years prior to RA onset, at a young age, similar to primary RP (uncommon); (2) RP and RA onset within a similar timeframe (within 4 yrs) with no obvious effect on RA severity (50% of RP in RA falls into this category); and (3) RP onset years after RA, which may be correlated to worse severity of RA, but could be linked to longer disease duration (40% of RP in RA).

REFERENCES

1. Gordon DA, Hastings DE. Clinical features of rheumatoid arthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. 3rd ed. Toronto: Mosby; 2003:765-80.
2. Carroll GJ, Withers K, Bayliss CE. The prevalence of Raynaud's syndrome in rheumatoid arthritis. Ann Rheum Dis 1981;40:567-70.
3. Grassi W, Blasetti P, Core P, Cervini C. Raynaud's phenomenon in rheumatoid arthritis. Br J Rheumatol 1994;33:139-41.
4. Saraux A, Allain J, Guedes C, Baron D, Youinou P, Le Goff P. Raynaud's phenomenon in rheumatoid arthritis. Br J Rheumatol 1996;35:752-4.
5. Bartelink ML, Wollersheim H, van de Lisdonk E, Spruijt R, van Weel C. Prevalence of Raynaud's phenomenon. Neth J Med 1992;41:149-52.
6. Feigenbaum SL, Masi AT, Kaplan SB. Prognosis in rheumatoid arthritits. A longitudinal study of newly diagnosed younger adult patients. Am J Med 1979;66:377-84.
7. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
8. Rychlik-Golema W, Mastej K, Adamiec R. The role of endothelin-1 and selected cytokines in the pathogenesis of Raynaud's phenomenon associated with systemic connective tissue diseases. Int Angiol 2006;25:221-7.
9. Schwarz EM, Looney RJ, Drissi MH, et al. Autoimmunity and bone. Ann NY Acad Sci 2006;1068:275-83.
10. Cotaggio LJ, Evoson G, Harkness JA, Madison PJ. The arthropathy of systemic sclerosis (scleroderma); comparison with mixed connective tissue disease. Clin Exp Rheumatol 1983;1:101-12.
11. Leris RA, Adams JP, Gerber NL, Decker JL, Parsons DB. The hand in mixed connective tissue disease. J Hand Surg Am 1978;3:217-22.
12. Youinou P, Pennec Y-L, Katsikis P, Jouquan J, Fauquert P, Le Goff P. Raynaud's phenomenon in primary Sjögren's syndrome. Br J Rheumatol 1990;29:205-7.
13. Kraus A, Caballero-Uribe C, Jakez J, Villa AR, Alarcón-Segovia D. Raynaud's phenomenon in primary Sjögren's syndrome. Association with other extraglandular manifestations. J Rheumatol 1992;19:1572-4.
14. Leppert J, Åberg H, Ringqvist I, Sörensson S. Raynaud's phenomenon in a female population: prevalence and association with other conditions. Angiology 1987;38:871-7.
15. Wagner U, Pierer M, Kaltenhäuser S, et al. Clonally expanded CD4+CD28null T cells in rheumatoid arthritis use distinct combinations of T cell receptor BV and BJ elements. Eur J Immunol 2003;33:79-84.
16. Chikanza IC, Stein M, Lutalo S, Gibson T. The clinical, serological and radiological features of rheumatoid arthritis in ethnic black Zambabwean and British Caucasian patients. J Rheumatol 1994;21:2011-5.