ISSN: 2573-9565

Research Article

Journal of Clinical Review & Case Reports

Correlations between Hand Ultrasonography Changes and Autoantibody Profile in Patients with Systemic Sclerosis

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Submitted: 01 Nov 2018; **Accepted**: 07 Nov 2018; **Published**: 15 Nov 2018

Abstract

Aim: *To assess hand ultrasonography changes in systemic sclerosis (Ssc) patients and find a potential correlation of autoantibody profile*

Materials and method: *59 SSc patients, 40.7% dsSSc, 59.3% lcSSc, were hands US examinations, laboratory test, ESR, CRP, anti-Scl70, ACA, anti-RNAP III antibodies, anti-CCP, RF.*

Results: *Sclerosing tenosynovitis occured significantly more frequently in dcSSc patients than in lcSSC: in 4 out of 24 (16.7%) with dcSSc vs none (0%) out of 35 with lcSSc (p=0.0233). Anti-Scl70-positive patients increase ESR and CRP was observed – 61.5% (p=0.0014) and 29.0% (p=0.0420) respectively. Swelling in the hands soft tissue in 7 (21.9%) out of 32 anti-Scl70-positive patients vs 1 (13.7%) out of 27 anti-Scl70-negative (p=0.06) were observed. Sclerosing tenosynovitis occured only in anti-Scl70-positive patients. Inflammatory tenosynovitis occured statistically significantly often in males (in 3 (33.3%) out of 9) than in females (in 1 (2%) out of 50) (p=0.0095). It was observed that synositis, inflammatory and sclerosing tenosynovitis, severe inflammation in the hands soft tissue US examination occured statistically significantly often in patients with dsSSc (p=0.0006) as well as positive anti-Scl70 (p<0.0001), and significantly less than in ACA-positive. Synovitis occured in 20 (33.9%) out of 59 patients with Ssc. No patient was found to be anti-CCP antibody positive.*

Conclusion: *The hand ultrasonography features correlate with the clinical picture of SSc as well as the antibody profile, hand US may be used as a tool to assess the disease activity, as well as a predictive factor during the course of the disease.*

Keywords: Systemic Sclerosis, Ant-Ccp, Synovitis, Ultrasonography, Arthritis

Introduction

Systemic sclerosis (SSc) is a disease with a high mortality rate, which has not seen drastic changes in the last 40 years [1]. SSc is characterized by a highly heterogenous group of clinical features. These features differ from patient to patient, making diagnosis challenging, as well as initiating the appropriate treatment [2]. Diffuse joint involvement is seen often, and may promote a differential diagnosis [3-6]. Synovitis and the occurrence of digital ulcers, all serve as prognostic factors and indicate a decreased survival rate [4, 7, 8]. However, clinical evaluation of the joint structure, as opposed to changes seen on the skin, is limited due to skin involvement in SS. Therefore, hand joint pathology can only be assessed using ultrasonography [9, 10]. Clinical evaluation during physical exam may not be enough to fully assess this. Despite this, the clinical necessity of using US for hand pathology assessment has not been determined as of yet [10]. Also, the relationship between changes seen on US of the hands, and specific features of SSc, remain unclear.

The aim of this study is to investigate a potential correlation between US changes in the hand and the type of autoantibody and type of systemic sclerosis present.

Materials and Method

Patients

The study included 59 patients with SSc, all who met the ACR/EULAR criteria from 2013 [11]. The patients were further divided into dcSSc and lcSSc. The following features were taken into account: age, sex, type of SSc, duration of Raynauds phenomenon, time of SSc diagnosis, physical exam of hands, serological parameters: anti-centromere antibody [ACA], anti-topoisomerase I [anti- Scl-70], anti-RNA polimerase III [anti-RNAP III], anti–cyclic citrullinated peptide [anti-CCP] antibodies, rheumatoid factor [RF], inflammatory markers [CRP, ESR], USG of hands.

Physical exam

Physical exam was performed by one examiner. Tender and swollen joints on palpation were examined in the hands.

US examination

US was performed by a radiologist specializing in musculo-skeletal imaging, using Siemens Acuson S 2000, linear probe with 14 MHz. Examined joints were assessed using a multidimensional projections and dynamic scanning, and evaluated for the presence of synovitis, tendinitis, tenosynovitis using grey-scale and power Dopler ultrasonography signal, intraarticular exudate, calcifications in soft tissue, degenerative changes in the form of osteophytes, carpal tunnel syndrome as swelling and inflammation of the median nerve. The power Doppler was set to 5 MHz frequency, PRF (pulse repetition frequency) from 488 to 977 Hz and the maximum level of gain excluding artefacts. Synovitis is defined as thickening of the synovium with low echogenicity compared to the tendon and with the presence of power Doppler signal. Synovitis is not taken into account in isolated episodes of thickening, without activity in the Doppler option. Tenosynovitis is defined as hypo echoic thickening of the tendon sheath on gray-scale and when present - with power Doppler US.

Both hands and wrists were assessed using US: metatarsophalangeals, proximal and distal interphalangeals, carpal joints, radio-carpal joint, distal radio-ulnar joint, inter-carpal joints, as well as per articular structures and soft tissue.

Laboratory examinations

CRP was assessed using an immunoturbidymetric technique, with strengthened latex and ESR–optic method. RF was assessed using turbid metric method. Anti-CCP antibodies were marked using electrochemical illumination. ACA, anti-Scl-70, anti-RNAP III was marked using Western Blot.

Statistical analysis

Measurable variables were presented using the mean arithmetic and standard deviations (normal distribution) or median and interquartile range (irregular distribution), as well as absolute and relative frequency (qualitative variables). The following tests were used: to compare the difference between mean variables - t – Student test was applied, the difference between medians-Mann–Whitney nonparametric test, to compare proportions-chi2 Pearson or Fisher test, if the number observed in the table was less than 5. Zero hypothesis verifying statistical significance $p<0.05$. Two-sided testing was applied. Statistical analysis was performed using SAS statistical packet, 9.2 versions.

Results

Investigation of population 59 patients with SSc was involved in this study. 84,7% females, average age 54.6 ± 12.8 years; 24 (40,7%) patients with diffuse SSc (dcSSc); average time from diagnosis 8.4 ± 7.8 years; average duration of Raynauds phenomenon 12.5 ± 10.0 years. Physical exam excluded swollen joints in all patients. Number of anti-Scl70 positive patients was 32 (54.2%); the number of ACA positive patients was 19 (32.2%). 9 (15, 2%) patients were ACA and anti-Scl70- negative, of which 3 had diffuse type of SSc (dcSSc). No patient was found to be anti-CCP positive. RF was present in 9 (15.2) patients, anti-RNAP III were positive in 6 (10%) patients. Inflammatory markers: ESR and CRP were evaluated in 21 (39.6) and 11 (19.3) patients, respectively.

Ultrasonography findings in all patients (100%), US hand examination showed degenerative changes in the form of osteophytes. Synovial proliferation was shown in 28 (47.5%) patients. In 24 (40.6%) of patients US showed mild swelling with concomitant mild inflammation activity confirmed using Dopper of soft tissue surrounding joints. However, in 8 (13.6%) patients soft tissue's swelling with severe activity in power Doppler signal was found. Synovitis was observed in 20 (33.9%) patients. This was characterized mainly by thickening of the synovial membrane and mild activity in power Doppler. In 9 (15.2%) patients, carpal tunnel was confirmed. Joint effusion was found in 8 (13.6%) patients. Calcifications in tissue occurred in 6 (10.1%) of patients. Tenosynovitis occurred in 4 (6.8%) patients, and was characterized by hypo echoic thickening of the tendon sheath with visible vascularization in power Doppler US – considered as inflammatory tenosynovitis. However, in another 4 (6.8%) of patients fibrotic changes were observed in tendon sheath without any power Doppler signal - considered as sclerosing tenosynovitis.

Comparison of results in patients with diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (lcSSc). Patients with dcSSC were statistically significantly younger than patients with lcSSc – average age ± SD 48.6 ± 12.8 years versus 58.7 ± 11.3 ($p=0.0022$). It was found that in patients with dcSSc, statistically more patients showed sclerosis of tendon sheaths on hand US than in patients with lcSSc - in 4 out of 24 (16.7%) patients with dcSSc versus none (0%) out of 35 patients with lcSSc ($p=0.0233$). No other significant changes were found in US imaging in these groups of patients.

Table 1: Comparison of results in patients with dcSSc and lcSSc

	dSSc n=24	lSSc n=35	P
Age (years) ± SD	48.6 ± 12.8	58.7 ± 11.3	0.0022
Time from diagnosis SSc (years), ± SD	8.2 ± 7.5	8.6 ± 8.2	0.8525
Female	20 (83.3)	30 (85.7)	1
Time from the onset Raynaud syndrome (years), ± SD	10.2 ± 8.9	10.6	0.1438
Autoantibody profile			
Anti-Scl-70 (+)	21 (87.5)	11 (31.4)	<0.0001
ACA (+)	1 (4.2)	18 (51.4)	<0.0001
Anti-RNAP III (+)	3 (12.5)	3 (8.8)	0.6838
Anti-CCP (+)	0	0	NA
Inflammatory markers			
ESR+	10 (52.6)	11 (32.3)	0.1478
CRP+	7 (30.4)	4 (11.8)	0.0981
US findings			
Synovitis	9 (37.5)	11 (31.4)	0.6284
Synovial proliferation	11 (45.8)	17 (48.6)	0.8361
Joint effusion	5 (20.8)	3 (8.6)	0.2508
Inflammatory tenosynovitis	2 (8.3)	2 (5.7)	1
Sclerosing tenosynovitis	4 (16.7)	0 (0)	0.0233

Swelling of soft tissue with severe inflammatory activity in PD	3 (12.5)	5 (14.3)	1
Except when otherwise indicated, values are the number (%). NA=not applicable			

Correlation of inflammatory parameters with autoantibodies

In patients with positive anti-Scl70, it was found that there was an increase in inflammatory parameters ESR and CRP: increase ESR was found in 16 (61.5%) out of 32 patients anti-Scl70-positive and only 5 (18.5%) out of 27 anti-Scl70-negative patients (p=0.0014); increased CRP was discovered in 9 (29.0%) out of 32 patients anti-Scl70-positive versus 2 (7.7%) out of 27 anti-Scl70-negative patients (p=0.0420).

Correlation of autoantibodies with hand changes seen on US In patients anti-Scl-70-positive it was observed tendency to occur more frequently the soft tissue's swelling with severe activity in PDUS: in 7 (21.9%) out of 32 patient's anti-Scl-70-positive versus 1 (13.7%) out of 27 anti-Scl-70-negative patients (p=0.06). Sclerosing tenosynovitis occurred in anti-Scl-70-positive patients only. No relationship was found between US hand features and anti-RNA polimerase III antibodie. Also, no statistically significant correlation was found in the presence of RF and pathological hand changes seen on US. No patient was found to be anti-CCP positive.

Table 2. Comparison of results in patients anti-Scl-70-negative and anti-Scl-70-positive

Age (years) ± SD	56.4±12.1	53.0±13.4	0.2894
Time from diagnosis SSc (years), median (range)	5.0 [2-14]	7.5 [1.5-16.0]	0.7138
Female	23 (85.2)	27(84.4)	1
ACA (+)	18 (66.7)	1(3.1)	<0.0001
Anti-RNAP III (+)	3 (11.5)	3(9.4)	1
Anti-CCP (+)	0	0	NA
Time from the onset Raynaud syndrome (years), median (range)	15 [5-20]	8.5 [3.0-21]	0.2626
dcSSc	3 (11.1)	21 (65.6)	<0.0001
lcSSc	24 (88.9)	11 (34.4)	
ESR+	5 (18.5)	16 (61.5)	0.0014
CRP+			
US findings			
Synovitis	6 (22.2)	14 (43.7)	0.0818
Synovial proliferation	12 (44.4)	16 (50.0)	0.6703
Joint effusion	3 (11.1)	5 (15.6)	0.7154
Inflammatory tenosynovitis	1 (3.7)	3 (9.4)	0.6175
Sclerosing tenosynovitis	0 (0.0)	4 (12.5)	0.1176
Swelling of soft tissue with severe inflammatory activity in PD	1 (13.7)	7 (21.9)	0.0595
Except when otherwise indicated, values are the number (%). NA=not applicable			

Correlation between US hand changes and clinical features of SSc. Inflammatory tenosynovitis was present statistically significant more common in male patients: (3 (33.3%) out of 9 males), than in female patients (1 (2%) out of 50 females) (p=0.0095). Sclerosing tenosynovitis was found statistically more often in patients with dcSSc type: 4 (100%) out of 4 patients with sclerosing pattern in tendon sheaths seen on hand US had dcSSc type (p=0.0233). Patients with synovial proliferation were found to be older than patients without SP: average age ± SD 58.7 ± 12.3 versus 50.9 ± 12.3 (p=0.0184).

Comparison between patients with the following hand pathologies seen on US–synovitis, inflammatory and sclerosing tenosynovitis, swelling and severe PD activity in soft tissues of the hand versus patients without the above-mentioned pathologies.

Table 3: Comparison between patients with the following hand pathologies seen on US – synovitis, inflammatory and sclerosing tenosynovitis, swelling and severe PD activity in soft tissues of the hand versus patients without the above-mentioned pathologies

	Absent n=20 (33,9)	Present n=39 (66,1)	p
Age (years) ± SD	57,2 ± 12,1	53,3 ± 13,2	0,2714
Female	19 (95,0)	31 (79,5)	0,148
Time from diagnosis SSc (years), median (range)	4,5 (2 – 12,0)	7,0 (2,0 -19,0)	0,2392
dcSSc	2 (10,0)	22 (56,4)	0,0006
Anti-Scl-70 (+)	2 (10,0)	30 (76,9)	<0,0001
ACA (+)	13 (65,0)	6 (15,4)	0,0001
Anti-RNAP III (+)	2 (10,5)	4 (10,3)	1
RF+	5 (25)	4 (10,8)	0,2532
CRP+	1 (5,0)	10 (27,0)	0,0761
OB+	6 (30,0)	15 (45,4)	0,2648
Except when otherwise indicated, values are the number (%)			

Patients with the above mentioned pathologies had a statistically significant increased presence of dcSSc type and presence of anti-Scl-70 antibodies, and a statistically significant decreased presence of ACA antibodies.

Discussion

In our practice, like other researchers, we found that besides typical tenosynovitis, that exists in other diseases as well, our patients with systemic sclerosis also exhibited sclerosing tenosynovitis that most probably is unique to systemic sclerosis [9,12]. It is possible that fibrotic changes in tendon sheaths are a consequence of a past inflammatory process within these structures. Rodnan et al. described tendon friction rubs as a result of fibrotic deposit in tendon sheaths as well as in fascia [13]. In Elhai et al. study tendon friction rubs occurred only in patients with tendon involvement seen on US, and patients with sclerosing tenosynovitis had a tendency of tendon friction rubs. Tendon friction rubs are a prognostic factor in the progression of systemic sclerosis in patients with early disease onset, as well as one of the criteria used in the disease activity index [8,14]. In routine everyday practice, it is possible to not diagnose tendon friction rubs in patients after clinical examination; however US will show this phenomenon. In our study, fibrotic changes in

tendon sheats occurred only in patients with anti-Scl-70 antibodies and diffuse cutaneous systemic sclerosis. It is unknown whether or not sclerosing tenosynovitis occurs only in this group of patients; a larger-scale study of patients would be needed. Future investigations involving the usefulness of presence of sclerosing pattern in tendon sheath in US imaging as a prognostic factor in diffuse cutaneous systemic sclerosis may be helpful.

Tendinitis and tenosynovitis with inflammatory activity in PDUS occurs more often in males. In epidemiological studies the following symptoms of systemic sclerosis occurred more often in males: myopathy, diffuse cutaneous systemic sclerosis, digital ulcers, primary pulmonary hypertension, proteinuria–the factors indicating severe disease prognosis [15]. Men are diagnosed with systemic sclerosis less frequently than women; however a worse disease prognosis occurs more often. It is possible that tendinitis/tenosynovitis seen on US may also be an indicator of a more aggressive disease progression. An interesting study would be a correlation between changes seen on US and organ involvement in the course of systemic sclerosis.

In our study we observed that anti-Scl-70 antibodies as well as diffuse cutaneous systemic sclerosis, correlated with hand changes seen on US, which are characteristic for active tenosynovitis, sclerosing tenosynovitis and high inflammatory activity in soft tissues seen on power Doppler. In past publications US mainly described bone, articular involvement, and the presence of calcifications in soft tissues. In this study we also included the inflammatory status as seen on power Doppler in the soft tissues of the hand. In our opinion, the above parameters may reflect a current and increasing inflammatory process in the course at the disease, as well as indicate an aggressive course of the disease.

No patient that took part in our study had identifiable anti-CCP antibodies, despite the presence of arthritis in the hands [16]. In Polimeni M et al. study anti-CCP antibodies were identified in 9 out of 78 (11.5%) patients with SSc, however it should be observed that out of that group of patients, 14.1% had overlapping diseases with systemic lupus erythematosus or polymyositis, which was not present in our study. In the above study no correlation was observed between the presence of anti-CCP antibodies and arthritis. The only observation made was arthralgia in patients with anti-CCP antibodies. These results not collide with the results from Santiago M. et al. as well as Ingegnoli F. et al. who observed a relationship between positive anti-CCP antibodies and joint inflammation in patients with SSc [17,18]. The study considered the value of identifying anti-CCP antibodies and arthritis in patients with SSc, the researchers concluded that high concentration of anti-CCP in patients with SSc combined with an increased level of other RA-related antibodies may help identify patients with overlapping SSc-RA [19]. The role of anti-CCP antibodies and their potential impact on arthritis in patients with Ssc remain unclear. It is possible that anti-CCP antibodies may be identified in patients with SSc who also suffer from an overlapping connective tissue disease, especially that in one fifth out of 1700 patients with diagnosed systemic sclerosis have identifiable symptoms of another overlapping connective tissue disease, due to the fact that anti-CCP antibodies may be present in other rheumatological disorders [20-22].
In our study, positive RF was present in 9 (15.8%) out of 57 patients with SSC. No significant correlation was observed between the presence of RF and the present of arthritis, type of SSc and other antibodies related with SSc-ACA, anti-Scl70, anti-RNA POL III.

In hand US examination synovitis was observed in 20 (33.9%) out of 59 patients with SSc. Similarly to Cuomo G. et al. study, no significant correlation was observed between synovitis in US and the clinical presentation of SSc, however unlike the above mentioned authors, in our results we did not observe a correlation between synovitis and the concentration of CRP [22]. In EUSTAR analysis, it was found that synovitis, defined as swollen and tenderness joints, was more common in patients with diffuse cutaneous type of systemic sclerosis. In this study it was observed that patients with arthritis and early systemic sclerosis had a higher probability of developing dcSSc type [4]. In our study, synovitis was diagnosed on US examination of the hand. It is possible that arthritis diagnosed during physical examination characterize more expanded inflammation, than synovitis observed only via imaging examinations, as well as it may represent a more aggressive inflammation, which may be confirmed via CRP concentrations in laboratory tests.

Our study did not take into account treatment in the patient examined, we do not know what influence pharmacotherapy may have on US results of the hands in patients with SSc.

To conclude, it is highly possible that some US hand changes correlate to the clinical picture of SSc as well as autoantibody profile. US hand examination in patients is not only useful to assess articular involvement, but as well as may be used as a tool to assess the current disease activity and describe predictive factors in the course of the disease. US is a more sensitive method used to find pathologies, than physical examination or X-ray, and it is a cheap and available method comparing to MRI, which may also be a very promising tool in detecting musculoskeletal pathologies [23, 24]. A useful future study would include a large group of patients with varying clinical pictures of SSc in similar time duration of disease.

References

1. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y (2012) Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology 51: 1017-1026.
2. Lee JJ, Pope JE (2016) Diagnosis and Management of Systemic Sclerosis: A Practical Approach. Drugs 76: 203-213.
3. Avouac J, Guerini H, Wipff J, Assous N, Chevrot A, et al. (2006) Radiological hand involvement in systemic sclerosis. Ann Rheum Dis 65: 1088-1092.
4. Avouac J, Walker U, Tyndall A, Kahan A, Matucci-Cerinic M, et al. (2010) Characteristics of joint involvement and relationships with systemic inflammation in systemic sclerosis: results from the EULAR Scleroderma Trial and Research Group (EUSTAR) database. J Rheumatol 37: 1488-1501.
5. La Montagna G, Sodano A, Capurro V, Malesci D, Valentini G (2005) The arthropathy of systemic sclerosis: a 12 month prospective clinical and imaging study. Skeletal Radiol 34: 35-41.
6. Avouac J, Mogavero G, Guerini H, Drapé JL, Mathieu A, et al. (2011) Predictive factors of hand radiographic lesions in systemic sclerosis: a prospective study. Ann Rheum Dis 70: 630-633.
7. Mihai C, Landewe R, van der Heijde D, Walker UA, Constantin PI, et al. Digital ulcers predict a worse disease course in patients with systemic sclerosis. Ann Rheum Dis 75: 681-686.

8. Avouac J, Walker UA, Hachulla E, Riemekasten G, Cuomo G, et al. (2016) Joint and tendon involvement predict disease progression in systemic sclerosis: a EUSTAR prospective study. Ann Rheum Dis 75: 103-109.
9. Elhai M, Guerini H, Bazeli R, Avouac J, Freire V, et al. (2012) Ultrasonography hand features in systemic sclerosis and correlates with clinical, biologic, and radiographic findings. Arthritis Care Res (Hoboken) 64: 1244-1249.
10. Cuomo G, Zappia M, Abignano G, Iudici M, Rotondo A, et al. (2009) Ultrasonographic features of the hand and wrist in systemic sclerosis. Rheumatology (Oxford) 48: 1414-1417.
11. Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, et al. (2013) 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Ann Rheum Dis 72: 1747-1755.
12. Freire V, Bazeli R, Elhai M, Campagna R, Pessis É, et al. (2013) Hand and wrist involvement in systemic sclerosis: US feature. Radiology 269: 824-830.
13. Rodnan GP, Medsger TA (1968) the rheumatic manifestations of progressive systemic sclerosis (scleroderma). Clin Orthop Relat Res 57: 8193.
14. Valentini G, Iudici M, Walker UA, Jaeger VK, Baron M, et al. (2017) The European Scleroderma Trials and Research group (EUSTAR) task force for the development of revised activity criteria for systemic sclerosis: derivation and validation of a preliminarily revised EUSTAR activity index. Ann Rheum Dis 76: 270-276.
15. Desbois AC, Cacoub P (2016) Systemic sclerosis: An update in 2016. Autoimmune Rev 15: 417-426.
16. Polimeni M, Feniman D, Skare TS, Nisihara RM (2012) Anti-cyclic citrullinated peptide antibodies in scleroderma patients. Clin Rheumatol 31: 877-880.
17. Santiago M, Baron M, Miyachi K, Fritzler MJ, Abu-Hakima M, et al. (2008) A comparison of the frequency of antibodies to cyclic citrullinated peptides using a third generation anti-CCP assay (CCP3) in systemic sclerosis, primary biliary cirrhosis and rheumatoid arthritis. Clin Rheumatol 27: 77-83.
18. Ingegnoli F1, Galbiati V, Zeni S, Meani L, Zahalkova L, et al. (2008) Use of antibodies recognizing cyclic citrullinated peptide in the differential diagnosis of joint involvement in systemic sclerosis.
19. Ueda-Hayakawa I, Hasegawa M, Kumada S, Tanaka C, Komura K, et al. (2010) Usefulness of anti-cyclic citrullinated peptide antibody and rheumatoid factor to detect rheumatoid arthritis in patients with systemic sclerosis. Rheumatology (Oxford) 49: 2135-2139.
20. Pakozdi A, Nihtyanova S, Moinzadeh P, Ong VH, Black CM, et al. (2011) Clinical and serological hallmarks of systemic sclerosis overlap syndromes. J Rheumatol 38: 2406-2409.
21. S Caterbi, O Bistoni, A Alunno, E Bartoloni, R Gerli (2015) Ant cyclic Citrullinated Peptide Antibodies in Patients with Rheumatic Diseases other than Rheumatoid Arthritis: Clinical or Pathogenic Significance? J Rheumatol 42: 1063-1064.
22. Payet J, Goulvestre C, Bialé L, Avouac J, Wipff J, et al. (2014) Ant cyclic citrullinated peptide antibodies in rheumatoid and no rheumatoid rheumatic disorders: experience with 1162 patients. J Rheumatol 41: 2395-2402.
23. Low AH, Lax M, Johnson SR, Lee P (2009) Magnetic resonance imaging of the hand in systemic sclerosis. J Rheumatol 36: 961-964.
24. Chitale S, Ciapetti A, Hodgson R, Grainger A, O'Connor P, et al. (2010) Magnetic resonance imaging and musculoskeletal ultrasonography detect and characterize covert inflammatory arthropathy in systemic sclerosis patients with arthralgia. Rheumatology 49: 2357-2361.